STN Search History

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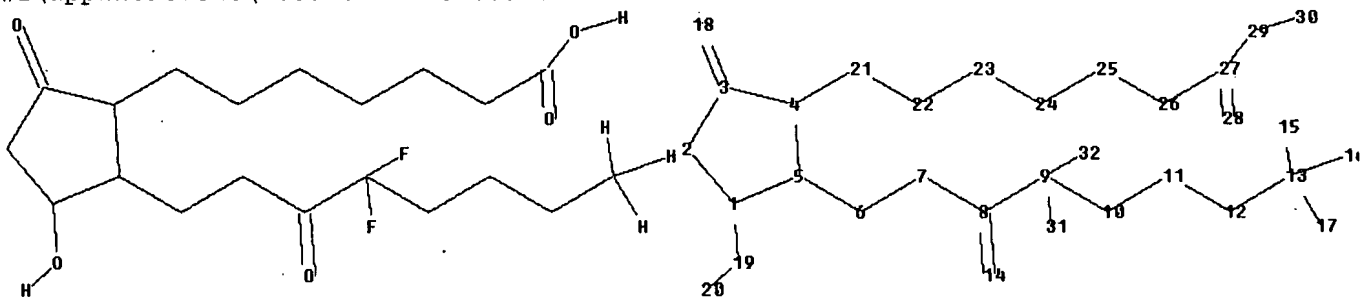

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1 2 3 4 5
chain bonds :
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ring bonds :
1-2 1-5 2-3 3-4 4-5
exact/norm bonds :
1-2 1-5 1-19 2-3 3-4 3-18 4-5 8-14
exact bonds :
4-21 5-6 6-7 7-8 8-9 9-10 9-31 9-32 10-11 11-12 12-13 13-15 13-16 13-17 19-20 21-22 22-23 23-24 24-25 25-26 26-27 29-30
normalized bonds :
27-28 27-29

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:CLASS 7:CLASS 8:CLASS 9:CLASS 10:CLASS 11:CLASS 12:CLASS 13:CLASS 14:CLASS 15:CLASS 16:CLASS 17:CLASS 18:CLASS 19:CLASS 20:CLASS 21:CLASS 22:CLASS 23:CLASS 24:CLASS 25:CLASS 26:CLASS 27:CLASS 28:CLASS 29:CLASS 30:CLASS 31:CLASS 32:CLASS

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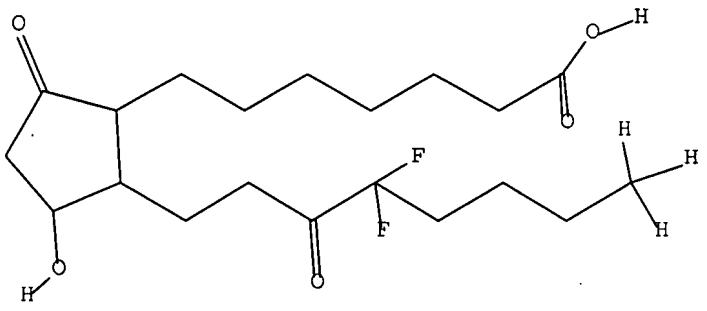

Structure attributes must be viewed using STN Express query preparation.

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SAMPLE SCREEN SEARCH COMPLETED -        4 TO ITERATE

100.0% PROCESSED         4 ITERATIONS                                0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:            4 TO      200
PROJECTED ANSWERS:               0 TO        0

L7             0 SEA SSS SAM L6

=> s l6 fam full
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SEARCH TIME: 00.00.01

L8             1 SEA FAM FUL L6

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ED   Entered STN:  18 Oct 1991
CN   Prostan-1-oic acid, 16,16-difluoro-11-hydroxy-9,15-dioxo-, (11α)-
     (CA INDEX NAME)
OTHER NAMES:
CN   Lubiprostone
CN   Ru 0211
FS   STEREOSEARCH
MF   C20 H32 F2 O5
SR   CA
LC   STN Files:   ADISINSIGHT, BIOSIS, CA, CAPLUS, CASREACT, CBNB, CHEMCATS,
       CIN, EMBASE, IMSDRUGNEWS, IMSPATENTS, IMSRESEARCH, PROMT, PROUSDDR,
       SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL

Absolute stereochemistry.
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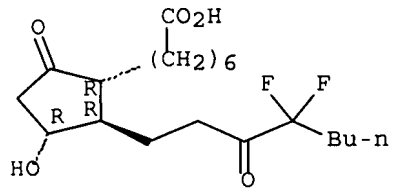

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

28 REFERENCES IN FILE CA (1907 TO DATE)
28 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> d hist

(FILE 'HOME' ENTERED AT 18:47:30 ON 28 NOV 2007)

FILE 'REGISTRY' ENTERED AT 18:47:42 ON 28 NOV 2007
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L2 0 S 16,16-DIFLUORO-13,14-DIHYDRO-15-KETO
L3 0 S DIFLUORO (20A) PGE
L4 0 S DIFLUORO (A) PGE
L5 9 S DIFLUORO (20A) PGE?
L6 STRUCTURE UPLOADED
L7 0 S L6
L8 1 S L6 FAM FULL

FILE 'CAPLUS, MEDLINE' ENTERED AT 19:17:36 ON 28 NOV 2007
L9 28 S L8

=> s (l8 or Lubiprostone) and obesity
L10 1 (L8 OR LUBIPROSTONE) AND OBESITY

=> d l10 ibib abs hitstr

L10 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:368933 CAPLUS Full-text
DOCUMENT NUMBER: 140:369355
TITLE: Prostaglandin compounds and method for their uses in the treatment of obesity
INVENTOR(S): Ueno, Ryuji
PATENT ASSIGNEE(S): Sucampo A.-G., Switz.
SOURCE: PCT Int. Appl., 36 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004037268	A1	20040506	WO 2003-JP13453	20031022

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LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM,
PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN,
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FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
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AU 2003274735	A1	20040513	AU 2003-274735		20031022
EP 1562604	A1	20050817	EP 2003-758747		20031022
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JP 2006506381	T	20060223	JP 2004-546433		20031022
NZ 539582	A	20070727	NZ 2003-539582		20031022
US 2005261373	A1	20051124	US 2005-531874		20050419
PRIORITY APPLN. INFO.:			US 2002-420336P	P	20021023
			WO 2003-JP13453	W	20031022

OTHER SOURCE(S): MARPAT 140:369355

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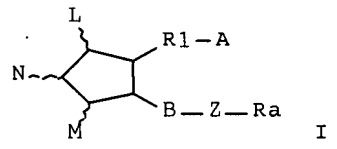


I

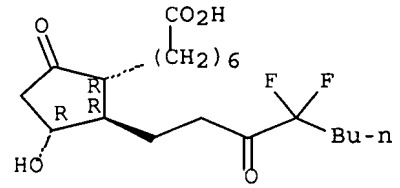
AB Provided is a compn. for treating obesity which comprises an effective amount of a prostaglandin compound, especially, a compound of formula (I).

IT 136790-76-6
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prostaglandin compds. and method for their uses in treatment of obesity)

RN 136790-76-6 CAPLUS

CN Prostan-1-oic acid, 16,16-difluoro-11-hydroxy-9,15-dioxo-, (11α)- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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=> s (l8 or Lubiprostone) and (obesity or fat or lipid)
L11          2 (L8 OR LUBIPROSTONE) AND (OBESITY OR FAT OR LIPID)

=> d l11 ibib abs hitstr 1-2

L11  ANSWER 1 OF 2  CAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:         2004:368933  CAPLUS Full-text
DOCUMENT NUMBER:          140:369355
TITLE:                    Prostaglandin compounds and method for their uses in
                          the treatment of obesity
INVENTOR(S):              Ueno, Ryuji
PATENT ASSIGNEE(S):       Sucampo A.-G., Switz.
SOURCE:                   PCT Int. Appl., 36 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.          DATE
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         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
             KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
             FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
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     CA 2502439            A1    20040506    CA 2003-2502439          20031022
     AU 2003274735         A1    20040513    AU 2003-274735           20031022
     EP 1562604            A1    20050817    EP 2003-758747           20031022
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
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     JP 2006506381         T     20060223    JP 2004-546433           20031022
     NZ 539582             A     20070727    NZ 2003-539582           20031022
     US 2005261373         A1    20051124    US 2005-531874           20050419
PRIORITY APPLN. INFO.:                       US 2002-420336P      P   20021023
                                             WO 2003-JP13453      W   20031022

OTHER SOURCE(S):          MARPAT 140:369355
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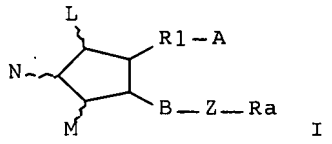
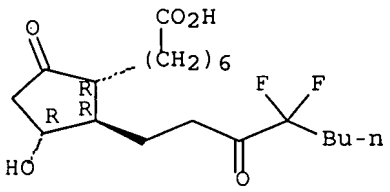


I

AB Provided is a compn. for treating obesity which comprises an effective amount of a prostaglandin compound, especially, a compound of formula (I).

IT 136790-76-6
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prostaglandin compds. and method for their uses in treatment of obesity)
RN 136790-76-6 CAPLUS
CN Prostan-1-oic acid, 16,16-difluoro-11-hydroxy-9,15-dioxo-, (11α)- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 2 OF 2 MEDLINE on STN
ACCESSION NUMBER: 2003410661 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 12949633
TITLE: Gateways to clinical trials.
AUTHOR: Bayes M; Rabasseda X; Prous J R
CORPORATE SOURCE: Prous Science, Barcelona, Spain.. mbayes@prous.com
SOURCE: Methods and findings in experimental and clinical pharmacology, (2003 Jul-Aug) Vol. 25, No. 6, pp. 483-506. Journal code: 7909595. ISSN: 0379-0355.
PUB. COUNTRY: Spain
DOCUMENT TYPE: Bibliography
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200403
ENTRY DATE: Entered STN: 3 Sep 2003
Last Updated on STN: 11 Mar 2004
Entered Medline: 10 Mar 2004

AB Gateways to Clinical Trials is a guide to the most recent clinical trials in current literature and congresses. The data in the following tables has been retrieved from the Clinical Studies Knowledge Area of Prous Science Integrity, the drug discovery and development portal, http://integrity.prous.com. This issue focuses on the following selection of drugs: ABT-510, ABX-EGF, acetyldinaline, ACIDFORM, acyline, afeletecan hydrochloride, anecortave acetate, apolizumab, l-arginine hydrochloride, asimadoline, atazanavir sufate, atlizumab; BMS-181176, BMS-188667; CAB-175, carnosine, CDP-870, CEP-701, CEP-7055, CGC-1072, ChimeriVax-JE, ciclesonide, cilomilast, clofarabine, combretastatin A-4 phosphate, cryptophycin 52; Duloxetine hydrochloride; E-5564, eculizumab, elcometrine, emtricitabine, ENO, epratuzumab, eszopiclone, everolimus; Fampridine, flurbiprofen nitroxybutyl ester; Garenoxacin mesilate, gestodene, GI-181771, gimatecan, gomiliximab; Halofuginone hydrobromide, hGH, hLM609; ICA-17043, IL-1 receptor type II, IMC-1C11, iodine (I131) tositumomab, irofulven, ISAtx-247; J591; L-778123, lanthanum carbonate Lasofoxifene tartrate, LDP-02, LE-AON, leteprinim potassium, lintuzumab, liraglutide, lubiprostone, lumiracoxib, lurtotecan, LY-450108, LY-451395; MAb G250, magnesium sulfate, MDX-210, melatonin, 2-methoxy-estradiol, monophosphoryl lipid A; NM-3, nolpitantium besilate; Ocinaplon, olpadronic acid sodium salt,

oral heparin; Palonosetron hydrochloride, pemetrexed disodium, PI-88, picoplatin, plevitrexed, polyphenon E, pramlintide acetate, pregabalin, prinomastat, pyrazoloacridine; Resiniferatoxin, rhEndostatin, roxifiban acetate; S-18886, siplizumab, sitaxsentan sodium, solifenacin succinate, SU-11248, SU-6668; Talampanel, TAPgen, testosterone transdermal gel, trabectedin; VEGF-2 gene therapy, visilizumab; ZD-6416, ZD-6474.

=> FIL STNGUIDE

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	174.43	362.64

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CA SUBSCRIBER PRICE	-23.40	-23.40

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FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Nov 23, 2007 (20071123/UP).

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SESSION WILL BE HELD FOR 120 MINUTES
STN INTERNATIONAL SESSION SUSPENDED AT 19:23:21 ON 28 NOV 2007

Connecting via Winsock to STN

Welcome to STN International! Enter x:x

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PASSWORD:
* * * * * * RECONNECTED TO STN INTERNATIONAL * * * * * *
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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
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=> fil caplus medline
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USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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=> d hist

     (FILE 'HOME' ENTERED AT 18:47:30 ON 28 NOV 2007)

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L2             0 S 16,16-DIFLUORO-13,14-DIHYDRO-15-KETO
L3             0 S DIFLUORO (20A) PGE
L4             0 S DIFLUORO (A) PGE
L5             9 S DIFLUORO (20A) PGE?
L6               STRUCTURE UPLOADED
L7             0 S L6
L8             1 S L6 FAM FULL

     FILE 'CAPLUS, MEDLINE' ENTERED AT 19:17:36 ON 28 NOV 2007
L9            28 S L8
L10            1 S (L8 OR LUBIPROSTONE) AND OBESITY
L11            2 S (L8 OR LUBIPROSTONE) AND (OBESITY OR FAT OR LIPID)

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     FILE 'CAPLUS, MEDLINE' ENTERED AT 19:42:12 ON 28 NOV 2007

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L13            0 (L8 OR LUBIPROSTONE) AND L12

=> s obesity
L14       147275 OBESITY

=> s l12 and l14
L15         2362 L12 AND L14

=> s l15 and pge
L16            2 L15 AND PGE

=> d ibib abs 1-2

L16  ANSWER 1 OF 2  CAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:         2006:218007  CAPLUS Full-text
DOCUMENT NUMBER:          145:1407
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TITLE: Differentiation-dependent regulation of the cyclooxygenase cascade during adipogenesis suggests a complex role for prostaglandins

AUTHOR(S): Xie, Y.; Kang, X.; Ackerman, W. E., IV; Belury, M. A.; Koster, C.; Rovin, B. H.; Landon, M. B.; Kniss, D. A.

CORPORATE SOURCE: The Ohio State University, Columbus, OH, USA

SOURCE: Diabetes, Obesity and Metabolism (2006), 8(1), 83-93
CODEN: DOMEF6; ISSN: 1462-8902

PUBLISHER: Blackwell Publishing Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Aim: A thorough understanding of the mechanisms of adipocyte differentiation and metabolism is important for the prevention and/or treatment of obesity and its complications, including type 2 diabetes mellitus. A complex role for prostaglandins (PGs) in adipogenesis is suggested. We examined the expression and cellular localization of enzymes in the cyclooxygenase (COX) cascade that synthesize PGs as well as the PG profile as a function of differentiation status in 3T3-L1 cells. Methods: Murine 3T3-L1 preadipocytes were used as a model for studies of adipocyte differentiation induced by a hormone cocktail and compared with the parental fibroblastic line NIH 3T3. Both cell lines were incubated in maintenance medium or differentiation medium. Nine days after differentiation, the expression of enzymes in the COX cascade was evaluated by immunoblot anal., reverse transcriptase- polymerase chain reaction (RT-PCR) and immunocytochem., and PG formation was examined using enzyme immunoassay. Results: A differentiation-dependent diminution of COX-1 and COX-2 mRNA and cognate proteins in 3T3-L1 cells was observed PG release, including PGE2, 6-keto PGF1α, PGD2 and 15d-PGJ2, significantly decreased following differentiation in 3T3-L1 cells (ANOVA/Tukey, $p < 0.05$). However, microsomal PGE synthase (mPGES) and lipocalin-type PGD synthase (L-PGDS) were selectively upregulated. Immunocytochem. revealed that COX-1 and COX-2 became intracellularly more diffuse upon differentiation, whereas mPGES was redistributed to the nuclear compartment. Conclusions: Regulation of PG formation and COX-2 expression in 3T3-L1 cells is differentiation- dependent and involves changes in the levels of gene expression of the individual isoforms as well as redistribution of the enzymes within cellular compartments.

REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 2 OF 2 MEDLINE on STN

ACCESSION NUMBER: 2005679744 MEDLINE Full-text

DOCUMENT NUMBER: PubMed ID: 16367886

TITLE: Differentiation-dependent regulation of the cyclooxygenase cascade during adipogenesis suggests a complex role for prostaglandins.

AUTHOR: Xie Y; Kang X; Ackerman W E 4th; Belury M A; Koster C; Rovin B H; Landon M B; Kniss D A

CORPORATE SOURCE: Department of Obstetrics and Gynecology, Laboratory of Perinatal Research, The Ohio State University, College of Medicine and Public Health, Columbus, OH 43210, USA.

CONTRACT NUMBER: HD35581 (NICHD)

SOURCE: Diabetes, obesity & metabolism, (2006 Jan) Vol. 8, No. 1, pp. 83-93.
Journal code: 100883645. ISSN: 1462-8902.

PUB. COUNTRY: England: United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, N.I.H., EXTRAMURAL)
(RESEARCH SUPPORT, NON-U.S. GOV'T)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200605
ENTRY DATE: Entered STN: 22 Dec 2005
Last Updated on STN: 4 May 2006
Entered Medline: 3 May 2006

AB AIM: A thorough understanding of the mechanisms of adipocyte differentiation and metabolism is important for the prevention and/or treatment of obesity and its complications, including type 2 diabetes mellitus. A complex role for prostaglandins (PGs) in adipogenesis is suggested. We examined the expression and cellular localization of enzymes in the cyclooxygenase (COX) cascade that synthesize PGs as well as the PG profile as a function of differentiation status in 3T3-L1 cells. METHODS: Murine 3T3-L1 preadipocytes were used as a model for studies of adipocyte differentiation induced by a hormone cocktail and compared with the parental fibroblastic line NIH 3T3. Both cell lines were incubated in maintenance medium or differentiation medium. Nine days after differentiation, the expression of enzymes in the COX cascade was evaluated by immunoblot analysis, reverse transcriptase- polymerase chain reaction (RT-PCR) and immunocytochemistry, and PG formation was examined using enzyme immunoassay. RESULTS: A differentiation-dependent diminution of COX-1 and COX-2 mRNA and cognate proteins in 3T3-L1 cells was observed. PG release, including PGE (2), 6-keto PGF(1alpha), PGD(2) and 15d-PGJ(2), significantly decreased following differentiation in 3T3-L1 cells (anova/Tukey, $p < 0.05$). However, microsomal PGE synthase (mPGES) and lipocalin-type PGD synthase (L-PGDS) were selectively upregulated. Immunocytochemistry revealed that COX-1 and COX-2 became intracellularly more diffuse upon differentiation, whereas mPGES was redistributed to the nuclear compartment. CONCLUSIONS: Regulation of PG formation and COX-2 expression in 3T3-L1 cells is differentiation-dependent and involves changes in the levels of gene expression of the individual isoforms as well as redistribution of the enzymes within cellular compartments.

=> d hist

(FILE 'HOME' ENTERED AT 18:47:30 ON 28 NOV 2007)

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L3 0 S DIFLUORO (20A) PGE
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L5 9 S DIFLUORO (20A) PGE?
L6 STRUCTURE UPLOADED
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L8 1 S L6 FAM FULL

FILE 'CAPLUS, MEDLINE' ENTERED AT 19:17:36 ON 28 NOV 2007
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L10 1 S (L8 OR LUBIPROSTONE) AND OBESITY
L11 2 S (L8 OR LUBIPROSTONE) AND (OBESITY OR FAT OR LIPID)

FILE 'STNGUIDE' ENTERED AT 19:22:52 ON 28 NOV 2007

FILE 'CAPLUS, MEDLINE' ENTERED AT 19:42:12 ON 28 NOV 2007
L12 16295 S PPAR
L13 0 S (L8 OR LUBIPROSTONE) AND L12
L14 147275 S OBESITY
L15 2362 S L12 AND L14
L16 2 S L15 AND PGE

```
=> s l15 and prostaglandin
L17         48 L15 AND PROSTAGLANDIN

=> d scan

L17   48 ANSWERS   CAPLUS  COPYRIGHT 2007 ACS on STN
CC    2-9 (Mammalian Hormones)
TI    Prostaglandins promote and block adipogenesis through opposing
      effects on peroxisome proliferator-activated receptor γ
ST    prostaglandin adipogenesis peroxisome proliferator receptor
      gamma; PGJ2 PGF2 signal transduction adipocyte PPAR
IT    Adipose tissue
         (adipocyte; prostaglandins promote and block adipogenesis
         through opposing effects on peroxisome proliferator-activated receptor
         γ)
IT    Gene
         (expression; prostaglandins promote and block adipogenesis
         through opposing effects on peroxisome proliferator-activated receptor
         γ)
IT    Signal transduction, biological
         (prostaglandins promote and block adipogenesis through
         opposing effects on peroxisome proliferator-activated receptor γ)
IT    Phosphorylation, biological
         (receptor; prostaglandins promote and block adipogenesis
         through opposing effects on peroxisome proliferator-activated receptor
         γ)
IT    Peroxisome proliferator-activated receptors
      RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL
      (Biological study); PROC (Process)
         (γ; prostaglandins promote and block adipogenesis
         through opposing effects on peroxisome proliferator-activated receptor
         γ)
IT    551-11-1, PGF2α   60203-57-8, PGJ2   142243-02-5, Mitogen-activated
      protein kinase
      RL: BAC (Biological activity or effector, except adverse); BPR (Biological
      process); BSU (Biological study, unclassified); BIOL (Biological study);
      PROC (Process)
         (prostaglandins promote and block adipogenesis through
         opposing effects on peroxisome proliferator-activated receptor γ)

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):0

=> d ibib abs hitstr 1-48

L17  ANSWER 1 OF 48  CAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:         2007:790342  CAPLUS Full-text
DOCUMENT NUMBER:          147:160531
TITLE:                    Prostaglandin reductase inhibitors for
                          treatment of peroxisome proliferator-activated
                          receptor-related diseases
INVENTOR(S):              Lin, Rong-Hwa; Lin, Leewen; Lin, Shih-Yao; Lee,
                          Shu-Hua
PATENT ASSIGNEE(S):       Abgenomics Corporation, Taiwan
SOURCE:                   PCT Int. Appl., 33pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
```

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2007082178	A2	20070719	WO 2007-US60213	20070108

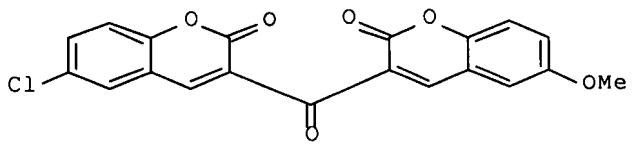
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2006-756734P P 20060106

OTHER SOURCE(S): CASREACT 147:160531; MARPAT 147:160531

GI



I

AB A method of inhibiting 15-keto prostaglandin-Δ13-reductase 2 by contacting the enzyme with an aryl compound is disclosed. Also disclosed are methods of treating peroxisome proliferator-activated receptor (PPAR)-related diseases and lowering blood glucose levels by administering to a subject in need thereof an effective amount of such an aryl compound PPAR-related diseases include type II diabetes, obesity, dyslipidemia, heart disease, inflammatory disease, and cancer. Thus, compound I inhibited human 15-keto prostaglandin-Δ13-reductase activity in in vitro assays and significantly reduced blood glucose levels in diabetic mice.

L17 ANSWER 2 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2007:397495 CAPLUS Full-text

DOCUMENT NUMBER: 146:440146

TITLE: Preadipocyte response and impairment of differentiation in an inflammatory environment

AUTHOR(S): Poulain-Godefroy, Odile; Froguel, Philippe

CORPORATE SOURCE: CNRS 8090, Institute of Biology, Pasteur Institute, Lille, 59021, Fr.

SOURCE: Biochemical and Biophysical Research Communications (2007), 356(3), 662-667
CODEN: BBRCA9; ISSN: 0006-291X

PUBLISHER: Elsevier

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Recent reports suggest the potential role of toll-like receptor 4 (TLR4) in initiation of inflammatory responses and fatty acid-induced insulin resistance. The authors describe here the synthesis of pro-inflammatory

products in 3T3-L1 preadipocyte cell line after stimulation with lipopolysaccharide (LPS), a TLR4 agonist. Expression profiles of mRNA coding for IL6, CCL2, CCL5, CCL11, NOS2, and PTGS2 demonstrated a higher responsiveness to LPS of these transcripts in preadipocytes than in fully differentiated adipocytes, confirming inflammatory features of preadipocytes. IL6, CCL2, CCL5 and CCL11 were secreted in 3T3-L1 supernatants within 4 h after LPS stimulation. In addition, continuous exposure to LPS during adipocyte differentiation impaired this process as was demonstrated by anal. of mRNA profiles of lipogenesis enzymes (FABP4, GPD1, LPL), adipokines (adiponectin, resistin, visfatin, leptin), and of the transcription factor PPAR.gamma.. Thus, toll-like receptor mediated activation could regulate maintenance of preadipocyte status, and inflammatory environment encountered in inflamed white adipose tissue.

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 3 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2007:175641 CAPLUS Full-text
DOCUMENT NUMBER: 146:244390
TITLE: Modulator of 15-keto prostaglandin -Δ13-reductase for treating peroxisome proliferators-activated receptors related diseases
INVENTOR(S): Lin, Rong-Hwa; Chuang, Lee-Ming
PATENT ASSIGNEE(S): Taiwan
SOURCE: U.S. Pat. Appl. Publ., 20pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2007037193	A1	20070215	US 2006-500579	20060808
EP 1803809	A2	20070704	EP 2006-291283	20060808
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, MK, YU				
JP 2007061093	A	20070315	JP 2006-218187	20060810
SG 130141	A1	20070320	SG 2006-5449	20060810
CA 2553115	A1	20070212	CA 2006-2553115	20060811
NO 2006003652	A	20070213	NO 2006-3652	20060811
AU 2006203479	A1	20070301	AU 2006-203479	20060811
CN 1916167	A	20070221	CN 2006-10109801	20060814
BR 2006003206	A	20070515	BR 2006-3206	20060814

PRIORITY APPLN. INFO.: US 2005-707897P P 20050812
OTHER SOURCE(S): MARPAT 146:244390

AB Provided is a method of treating a peroxisome proliferators-activated receptors related disease by administering to a subject in need thereof an effective amount of a modulator of 15-keto prostaglandin -Δ13-reductase PGR3/ZADH2 (zinc binding alc. dehydrogenase 2). Also disclosed are methods of identifying a compound for inhibiting activity of the reductase and of lowering blood glucose levels by administering to a subject an effective amount of a reductase inhibitor. Further provided are the protein and cDNA sequences of human and mouse zinc binding alc. dehydrogenase. Prostaglandin such as 15-keto PGE2 and 15-keto PGF2α enhanced endogenous PPAR.gamma. activity in adipocytes.

L17 ANSWER 4 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2007:65434 CAPLUS Full-text
DOCUMENT NUMBER: 146:99690
TITLE: Essential fatty acids - a review
AUTHOR(S): Das, Undurti N.
CORPORATE SOURCE: UND Life Sciences, Shaker Heights, OH, 44120, USA
SOURCE: Current Pharmaceutical Biotechnology (2006), 7(6), 467-482
CODEN: CPBUBP; ISSN: 1389-2010
PUBLISHER: Bentham Science Publishers Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Essential fatty acids (EFAs): cis-linoleic acid (LA) and α-linolenic acid (ALA) are essential for humans and their deficiency is rare in humans due to their easy availability in diet. EFAs are metabolized to their resp. long-chain metabolites: dihomo-gamma-linolenic acid (DGLA), and arachidonic acid (AA) from LA; and eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) from ALA. Some of these long-chain metabolites form precursors to resp. prostaglandins (PGs), thromboxanes (TXs), and leukotrienes (LTs), lipoxins (LXs) and resolvins. EFAs and their metabolites may function as endogenous angiotensin converting enzyme and HMG-CoA reductase inhibitors, nitric oxide enhancers, anti-hypertensives, and anti-atherosclerotic mols. EFAs react with nitric oxide (NO) to yield resp. nitroalkene derivs. that have cell-signaling actions via ligation and activation of peroxisome proliferator-activated receptors (PPARs). In several diseases such as obesity, hypertension, diabetes mellitus, coronary heart disease, alcoholism, schizophrenia, Alzheimer's disease, atherosclerosis, and cancer the metabolism of EFAs is altered. Thus, EFAs and their derivs. have significant clin. implications.

REFERENCE COUNT: 180 THERE ARE 180 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 5 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:1163767 CAPLUS Full-text
DOCUMENT NUMBER: 146:20697
TITLE: A novel positive feedback loop between peroxisome proliferator-activated receptor-δ and prostaglandin E2 signaling pathways for human cholangiocarcinoma cell growth
AUTHOR(S): Xu, Lihong; Han, Chang; Wu, Tong
CORPORATE SOURCE: Department of Pathology, University of Pittsburgh School of Medicine, Pittsburgh, PA, 15213, USA
SOURCE: Journal of Biological Chemistry (2006), 281(45), 33982-33996
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Peroxisome proliferator-activated receptor-δ (PPAR.delta.) is a nuclear receptor implicated in lipid oxidation and the pathogenesis of obesity and diabetes. This study was designed to examine the potential effect of PPAR.delta. on human cholangiocarcinoma cell growth and its mechanism of actions. Overexpression of PPAR δ or activation of PPAR.delta. by its pharmacol. ligand, GW501516, at low doses (0.5-50 nM) promoted the growth of three human cholangiocarcinoma cell lines (CCLP1, HuCCT1, and SG231). This effect was mediated by induction of cyclooxygenase-2 (COX-2) gene expression and production of prostaglandin E2 (PGE2) that in turn transactivated

epidermal growth factor receptor (EGFR) and Akt. In support of this, inhibition of COX-2, EGFR, and Akt prevented the PPAR δ-induced cell growth. Furthermore, PPAR.delta. activation or PGE2 treatment induced the phosphorylation of cytosolic phospholipase A2α (cPLA2α), a key enzyme that releases arachidonic acid (AA) substrate for PG production via COX. Overexpression or activation of cPLA2α enhanced PPAR.delta. binding to PPAR.delta. response element (DRE) and increased PPAR δ reporter activity, indicating a novel role of cPLA2α for PPAR.delta. activation. Consistent with this, AA enhanced the binding of PPAR.delta. to DRE, in vitro, suggesting a direct role of AA for PPAR.delta. activation. In contrast, although PGE2 treatment increased the DRE reporter activity in intact cells, it failed to induce PPAR.delta. binding to DRE in cell-free system, suggesting that cPLA2α-mediated AA release is required for PGE2-induced PPAR.delta. activation. Taken together, these observations reveal that PPAR.delta. induces COX-2 expression in human cholangiocarcinoma cells and that the COX-2-derived PGE2 further activates PPAR.delta. through phosphorylation of cPLA2α. This pos. feedback loop plays an important role for cholangiocarcinoma cell growth and may be targeted for chemoprevention and treatment.

REFERENCE COUNT: 69 THERE ARE 69 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 6 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2006:1131660 CAPLUS Full-text

DOCUMENT NUMBER: 146:79806

TITLE: Activated human T lymphocytes express cyclooxygenase-2 and produce proadipogenic prostaglandins that drive human orbital fibroblast differentiation to adipocytes

AUTHOR(S): Feldon, Steven E.; O'Loughlin, Charles W.; Ray, Denise M.; Landskroner-Eiger, Shira; Seweryniak, Kathryn E.; Phipps, Richard P.

CORPORATE SOURCE: Departments of Ophthalmology, University of Rochester School of Medicine and Dentistry, Rochester, NY, USA

SOURCE: American Journal of Pathology (2006), 169(4), 1183-1193
CODEN: AJPAA4; ISSN: 0002-9440

PUBLISHER: American Society for Investigative Pathology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The differentiation of preadipocyte fibroblasts to adipocytes is a crucial process to many disease states including obesity, cardiovascular, and autoimmune diseases. In Graves' disease, the orbit of the eye can become severely inflamed and infiltrated with T lymphocytes as part of the autoimmune process. The orbital fibroblasts convert to fat-like cells causing the eye to protrude, which is disfiguring and can lead to blindness. Recently, the transcription factor peroxisome proliferator activated receptor (PPAR)-γ and its natural (15d-PGJ2) and synthetic (thiazolidinedione-type) PPAR-γ agonists have been shown to be crucial to the in vitro differentiation of preadipocyte fibroblasts to adipocytes. We show herein several novel findings. First, that activated T lymphocytes from Graves' patients drive the differentiation of PPAR-γ-expressing orbital fibroblasts to adipocytes. Second, this adipogenic differentiation is blocked by nonselective small mol. cyclooxygenase (Cox)-1/Cox-2 inhibitors and by Cox-2 selective inhibitors. Third, activated, but not naive, human T cells highly express Cox-2 and synthesize prostaglandin D2 and related prostaglandins that are PPAR-γ ligands. These provocative new findings provide evidence for how activated T lymphocytes, through production of PPAR-γ ligands, profoundly influence human fibroblast differentiation to adipocytes. They also suggest the possibility

that, in addition to the orbit, T lymphocytes influence the deposition of fat in other tissues.

REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 7 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:958379 CAPLUS Full-text
DOCUMENT NUMBER: 145:484376
TITLE: Depot-specific prostaglandin synthesis in human adipose tissue: A novel possible mechanism of adipogenesis
AUTHOR(S): Quinkler, Marcus; Bujalska, Iwona J.; Tomlinson, Jeremy W.; Smith, Dave M.; Stewart, Paul M.
CORPORATE SOURCE: Division of Medical Sciences, Institute of Biomedical Research, University of Birmingham, Queen Elizabeth Hospital, Birmingham, B15 2TH, UK
SOURCE: Gene (2006), 380(2), 137-143
CODEN: GENED6; ISSN: 0378-1119
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Despite the magnitude of the obesity epidemic, the mechanisms that contribute to increases in fat mass and to differences in fat depots are still poorly understood. Prostanoids have been proposed as potent adipogenic hormones, e.g. metabolites of prostaglandin J2 (PGJ2) bind and activate PPAR.gamma.. We hypothesize that an altered expression of enzymes in PGJ2 synthesis may represent a novel pathogenic mechanism in human obesity. We characterized adipose depot-specific expression of enzymes in PGJ2 synthesis, prostaglandin transporter and PPAR.gamma. isoforms. Paired omental and s.c. adipose tissue samples were obtained from 26 women undergoing elective abdominal surgery and gene expression examined in whole tissue and cultured preadipocytes using an Affymetrix cDNA microarray technique and validated with quant. real-time PCR. All enzymes involved in prostaglandin synthesis were expressed in both adipose tissues. Expression of prostaglandin synthase-1 (PGHS1), prostaglandin D synthase (PTGDS), human prostaglandin transporter (hPGT) and PPAR.gamma.2 was higher in OM adipose tissue compared to SC, whereas 17β-hydroxysteroid dehydrogenase 5 (AKR1C3) showed predominance in SC adipose tissue. In SC adipose tissue, PGHS1 mRNA expression increased with BMI. The differential, depot-specific expression of key enzymes involved in transport, synthesis and metabolism of prostaglandins may have an important impact upon fat cell biol. and may help to explain some of the observed depot-specific differences. In addition, the pos. correlation between PGHS1 and BMI offers the novel hypothesis that the regulation of PG synthesis may have a role in determining fat distribution in human obesity.

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 8 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:914186 CAPLUS Full-text
DOCUMENT NUMBER: 145:389177
TITLE: PPAR.gamma. antagonists reverse the inhibition of neural antigen-specific Th1 response and experimental allergic encephalomyelitis by ciglitazone and 15-deoxy-Δ12,14-prostaglandin J2
AUTHOR(S): Raikwar, Himanshu P.; Muthian, Gladson; Rajasingh, Johnson; Johnson, Caroline N.; Bright, John J.
CORPORATE SOURCE: Department of Neurology, Vanderbilt University Medical Center, Nashville, TN, 37212, USA
SOURCE: Journal of Neuroimmunology (2006), 178(1-2), 76-86
CODEN: JNRIDW; ISSN: 0165-5728

PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Peroxisome proliferator-activated receptor-gamma is a nuclear receptor transcription factor that regulates cell growth, differentiation, and homeostasis. PPAR.gamma. agonists were used to treat obesity, diabetes, cancer, and inflammation and recent studies have shown the protective effects of PPAR.gamma. agonists on exptl. allergic encephalomyelitis (EAE), a Th1 cell-mediated autoimmune disease model of multiple sclerosis (MS). Our studies have further demonstrated that the PPAR.gamma. agonists, 15d-PGJ2 and ciglitazone, inhibit EAE through blocking IL-12 signaling leading to Th1 differentiation and the PPAR.gamma. deficient heterozygous mice (PPAR.gamma.+/-) or those treated with PPAR.gamma. antagonists develop an exacerbated EAE in association with an augmented Th1 response. In this study, we show that the PPAR.gamma. antagonists, Bisphenol A diglycidyl ether (BADGE) and 2-chloro-5-nitro-N- (4-pyridyl)benzamide (T0070907), reverse the inhibition of EAE by the PPAR.gamma. agonists, ciglitazone and 15-deoxy-Δ12,14- prostaglandin J2, in C57BL/6 wild-type and PPAR γ+/- mice. The reversal of EAE by BADGE and T0070907 was associated with restoration of neural antigen-induced T cell proliferation, IFNγ production and Th1 differentiation inhibited by ciglitazone and 15d-PGJ2. These results suggest that ciglitazone and 15d-PGJ2 ameliorate EAE through PPAR.gamma.-dependent mechanisms and further confirm a physiol. role for PPAR.gamma. in the regulation of CNS inflammation and demyelination in EAE.

REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 9 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:385868 CAPLUS Full-text
DOCUMENT NUMBER: 144:426192
TITLE: Use of parathyroid hormone-related protein (PTHrP) and other PPAR.gamma. ligands in the diagnosis and treatment of chronic lung disease and other hyperoxia-induced pathologies
INVENTOR(S): Torday, J. S.; Rehan, Virender K.; Mink, Richard
PATENT ASSIGNEE(S): Los Angeles Biomedical Research Institute At Harbor Ucla Medical Center, USA
SOURCE: U.S. Pat. Appl. Publ., 75 pp., Cont.-in-part of U.S. Ser. No. 352,768.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2006089388	A1	20060427	US 2005-218299	20050831
US 2004072875	A1	20040415	US 2003-352768	20030127
US 6992093	B2	20060131		
WO 2003092685	A1	20031113	WO 2003-US13481	20030501

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,

BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2005215606	A1	20050929	US 2005-513474		20050518
PRIORITY APPLN. INFO.:			US 2002-377665P	P	20020502
			US 2002-421615P	P	20021025
			US 2003-352768	A2	20030127
			WO 2003-US13481	W	20030501
			US 2005-513474	A1	20050518

AB This invention pertains to the discovery that parathyroid hormone-related protein (PTHrP) can be used to detect, monitor, and/or treat chronic lung diseases. In particular, it was discovered that PTHrP levels in broncho-alveolar lavage are indicative of lung "health" and "disease, and can be used to predict lung disease in patients at risk of chronic lung disease and/or to evaluate the efficacy of a ventilation regime. In the absence of PTHrP signaling through Protein Kinase A, the lung interstitial fibroblasts revert to myofibroblasts, the signature cell-type for fibrosis and alveolar dysfunction. This invention provides a method of inhibiting lipofibroblast to myofibroblasts transdifferentiation in a mammal by administering a PPAR.gamma. ligand. Also provided is a kit for mitigating one or more symptoms of a condition characterized by transdifferentiation of lipofibroblasts to myofibroblasts; the kit typically includes a PPAR.gamma. ligand. Also provided is a method of screening for an agent that mitigates one or more symptoms of a condition characterized by transdifferentiation of lipofibroblasts.

L17 ANSWER 10 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:	2006:383580 CAPLUS Full-text
DOCUMENT NUMBER:	144:404429
TITLE:	A method using farnesoid X receptor (FXR) agonists with PPAR agonists for reducing drug-induced adverse side effects in a patient
INVENTOR(S):	Fiorucci, Stefano; Pellicciari, Roberto; Pruzanski, Mark
PATENT ASSIGNEE(S):	Intercept Pharmaceuticals Inc., USA
SOURCE:	PCT Int. Appl., 35 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006044391	A1	20060427	WO 2005-US36536	20051014
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
US 2006252670	A1	20061109	US 2005-250298	20051013
AU 2005295888	A1	20060427	AU 2005-295888	20051014
CA 2584284	A1	20060427	CA 2005-2584284	20051014
EP 1814582	A1	20070808	EP 2005-807696	20051014

R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR

PRIORITY APPLN. INFO.: US 2004-619381P P 20041014
WO 2005-US36536 W 20051014

AB The invention relates to the discovery that farnesoid X receptor (FXR) agonists can be used in combination with peroxisome proliferation activated receptor γ (PPAR.gamma.) agonists to reduce drug-induced adverse side effects in patients suffering from conditions such as insulin resistance, Type II diabetes, metabolic syndrome, non-alc. fatty liver disease (NAFLD), non-alc. steatohepatitis (NASH), and heart disease. Particularly, the invention encompasses methods for treating patients suffering from drug-induced adverse side effects with selective PPAR.gamma., dual PPARa/γ and pan PPAR α/γ/δ agonists in combination with FXR agonists.

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 11 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:303828 CAPLUS Full-text
DOCUMENT NUMBER: 144:409466
TITLE: WNT and cyclooxygenase-2 cross-talk accelerates adenoma growth
AUTHOR(S): Wang, Dingzhi; Mann, Jason R.; DuBois, Raymond N.
CORPORATE SOURCE: Department of Medicine, Vanderbilt University Medical Center and Vanderbilt-Ingram Cancer Center, Nashville, TN, USA
SOURCE: Cell Cycle (2004), 3(12), 1512-1515
CODEN: CCEYAS; ISSN: 1538-4101
PUBLISHER: Landes Bioscience
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Both Wnt and cyclooxygenase (COX)-2 pathways are activated in most sporadic and familial colorectal cancers, especially in those with chromosomal instability. We have recently shown that a common target of both signaling pathways, the peroxisome proliferator-activated receptor (PPAR)-δ, is involved in intestinal adenoma growth. Activation of this receptor by synthetic agonist (GW501516) or COX-2-derived prostaglandin E2 (PGE2) accelerates intestinal adenoma growth in ApcMin mice. Moreover, these effects are lost in ApcMin mice lacking PPAR.delta.. These findings implicate PPAR δ as a focal point of cross-talk between the Wnt and prostaglandin signaling pathways. Based on this work it looks as if PPAR.delta. agonists currently in development for treatment of dyslipidemias and obesity may increase the risk of tumor formation in humans. By contrast, antagonists of PPAR.delta. may provide a novel approach for prevention and treatment of colorectal cancer.

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 12 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:218007 CAPLUS Full-text
DOCUMENT NUMBER: 145:1407
TITLE: Differentiation-dependent regulation of the cyclooxygenase cascade during adipogenesis suggests a complex role for prostaglandins
AUTHOR(S): Xie, Y.; Kang, X.; Ackerman, W. E., IV; Belury, M. A.; Koster, C.; Rovin, B. H.; Landon, M. B.; Kniss, D. A.
CORPORATE SOURCE: The Ohio State University, Columbus, OH, USA
SOURCE: Diabetes, Obesity and Metabolism (2006), 8(1), 83-93
CODEN: DOMEF6; ISSN: 1462-8902
PUBLISHER: Blackwell Publishing Ltd.
DOCUMENT TYPE: Journal

LANGUAGE: English

AB Aim: A thorough understanding of the mechanisms of adipocyte differentiation and metabolism is important for the prevention and/or treatment of obesity and its complications, including type 2 diabetes mellitus. A complex role for prostaglandins (PGs) in adipogenesis is suggested. We examined the expression and cellular localization of enzymes in the cyclooxygenase (COX) cascade that synthesize PGs as well as the PG profile as a function of differentiation status in 3T3-L1 cells. Methods: Murine 3T3-L1 preadipocytes were used as a model for studies of adipocyte differentiation induced by a hormone cocktail and compared with the parental fibroblastic line NIH 3T3. Both cell lines were incubated in maintenance medium or differentiation medium. Nine days after differentiation, the expression of enzymes in the COX cascade was evaluated by immunoblot anal., reverse transcriptase- polymerase chain reaction (RT-PCR) and immunocytochem., and PG formation was examined using enzyme immunoassay. Results: A differentiation-dependent diminution of COX-1 and COX-2 mRNA and cognate proteins in 3T3-L1 cells was observed PG release, including PGE2, 6-keto PGF1α, PGD2 and 15d-PGJ2, significantly decreased following differentiation in 3T3-L1 cells (ANOVA/Tukey, $p < 0.05$). However, microsomal PGE synthase (mPGES) and lipocalin-type PGD synthase (L-PGDS) were selectively upregulated. Immunocytochem. revealed that COX-1 and COX-2 became intracellularly more diffuse upon differentiation, whereas mPGES was redistributed to the nuclear compartment. Conclusions: Regulation of PG formation and COX-2 expression in 3T3-L1 cells is differentiation-dependent and involves changes in the levels of gene expression of the individual isoforms as well as redistribution of the enzymes within cellular compartments.

REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 13 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2004:878382 CAPLUS Full-text

DOCUMENT NUMBER: 141:350161

TITLE: Preparation of azole compounds as PTP1B inhibitors

INVENTOR(S): Ikemoto, Tomoyuki; Tanaka, Masahiro; Yuno, Takeo; Sakamoto, Johei; Nakanishi, Hiroyuki; Nakagawa, Yuichi; Ohta, Takeshi; Sakata, Shohei; Morinaga, Hisayo

PATENT ASSIGNEE(S): Japan Tobacco Inc., Japan

SOURCE: PCT Int. Appl., 542 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

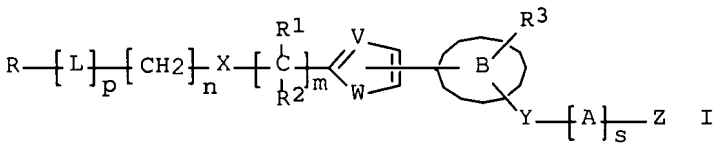
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004089918	A1	20041021	WO 2004-JP5119	20040409
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2004228565	A1	20041021	AU 2004-228565	20040409

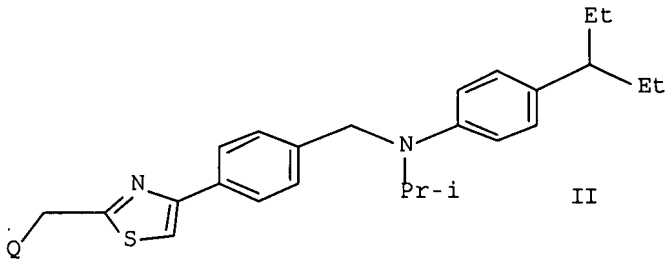
CA 2521830	A1	20041021	CA 2004-2521830	20040409
EP 1553091	A1	20050713	EP 2004-726765	20040409
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR				
BR 2004009136	A	20060425	BR 2004-9136	20040409
CN 1780823	A	20060531	CN 2004-80009487	20040409
JP 3819415	B2	20060906	JP 2005-505323	20040409
JP 2005272476	A	20051006	JP 2005-133755	20050428
US 2006122181	A1	20060608	US 2005-176846	20050707
NO 2005005246	A	20051221	NO 2005-5246	20051108
IN 2005CN02927	A	20070608	IN 2005-CN2927	20051109
PRIORITY APPLN. INFO.:			JP 2003-105267	A 20030409
			JP 2003-157590	A 20030603
			JP 2005-505323	A3 20040409
			WO 2004-JP5119	W 20040409

OTHER SOURCE(S): MARPAT 141:350161

GI



I



II

AB Title compds. I [V = N, CH; W = S, O; m = 0-2; R1, R2 = H, alkyl; X = NR4, etc.; R4 = H, alkyl; n = 0-4; p = 0, 1; L = CR20R21, etc.; R20 = H, alkyl, etc.; R21 = H, alkyl, etc.; R = CO2R19, etc.; R19 = H, alkyl; B = aryl, heteroaryl; R3 = H, halo, etc.; Y = O, etc.; s = 0, 1; A = (un)substituted alkylene with cycloalkyl; Z = cycloalkyl, etc.] were prepared For example, O-alkylation of 5-hydroxynicotinic acid Me ester with compound II [Q = Cl], e.g., prepared from 4-bromoacetylbenzoic acid in 5 steps, followed by saponification afforded compound II [3-carboxypyridin-5-yloxy] in 44.1% overall yield. In PTP1B (protein tyrosine phosphatase 1B) inhibition assays, the IC50 value of compound II [Q = 3-carboxypyridin-5-yloxy] was 0.28 μM. Compds. I are claimed useful for the treatment of obesity, diabetes, etc. Formulations are given.

REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 14 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:892610 CAPLUS Full-text
DOCUMENT NUMBER: 139:359241

TITLE: Use of parathyroid hormone-related protein (PTHrP) and other PPAR.gamma. ligands in the diagnosis and treatment of chronic lung disease and other hyperoxia-induced pathologies
INVENTOR(S): Torday, John S.; Rehan, Virender K.; Mink, Richard
PATENT ASSIGNEE(S): Harbor-UCLA Research and Education Institute, USA
SOURCE: PCT Int. Appl., 149 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003092685	A1	20031113	WO 2003-US13481	20030501
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004072875	A1	20040415	US 2003-352768	20030127
US 6992093	B2	20060131		
AU 2003232022	A1	20031117	AU 2003-232022	20030501
US 2005215606	A1	20050929	US 2005-513474	20050518
US 2006089388	A1	20060427	US 2005-218299	20050831

PRIORITY APPLN. INFO.:			
	US 2002-377665P	P	20020502
	US 2002-421615P	P	20021025
	US 2003-352768	A	20030127
	WO 2003-US13481	W	20030501
	US 2005-513474	A1	20050518

AB This invention pertains to the discovery that Parathyroid Hormone-related Protein (PTHrP) can be detect and/or stage, and/or treat chronic lung diseases. In particular, it was discovered that PTHrP levels in broncho-alveolar lavage are indicative of lung 'health' and 'disease', and can be used to predict lung disease in patients at risk of chronic lung disease and/or to evaluate the efficacy of a ventilation regime.
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 15 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:783895 CAPLUS Full-text
DOCUMENT NUMBER: 140:121903
TITLE: Peroxisome proliferator-activated receptor γ (PPAR.gamma.) ligands as bifunctional regulators of cell proliferation
AUTHOR(S): Na, Hye-Kyung; Surh, Young-Joon
CORPORATE SOURCE: College of Pharmacy, Laboratory of Biochemistry and Molecular Toxicology, Seoul National University, Seoul, 151-742, S. Korea
SOURCE: Biochemical Pharmacology (2003), 66(8), 1381-1391
CODEN: BCPCA6; ISSN: 0006-2952
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Peroxisome proliferator-activated receptor γ (PPAR.gamma.), a member of the ligand-activated nuclear receptor superfamily, plays a key role in mediating differentiation of adipocytes and regulating fat metabolism PPAR.gamma. has been implicated in the pathophysiol. of atherosclerosis, inflammation, obesity, diabetes, immune response, and aging. Recently, it has been shown that activation of PPAR.gamma. by J2 series cyclopentenone prostaglandins (cyPGs), especially 15-deoxy-Δ12,14- prostaglandin J2 (15d-PGJ2) or synthetic agents, such as antidiabetic thiazolidinediones, causes anti-proliferation, apoptosis, differentiation, and anti-inflammation of certain types of cancer cells. The anti-proliferative effects of PPAR.gamma. activators are associated with de novo synthesis of proteins involved in regulating the cell cycle and cell survival/death. Anti-inflammatory effects of 15d-PGJ2 are associated with interruption of nuclear factor-κB and subsequent blockade of inflammatory gene expression. Furthermore, 15d-PGJ2 at nontoxic doses induce expression of phase II detoxification or stress-responding enzymes, which may confer cellular resistance or adaptation to oxidative stress. The presence of a reactive α,β-unsatd. carbonyl moiety in the cyclopentenone ring of 15d-PGJ2 is important for part of biol. functions this cyPG has. Recently, attention has been focused on the anti-proliferative activity of nonsteroidal anti-inflammatory drugs (NSAIDs) in cancerous or transformed cells, which is mediated through interaction with PPAR.gamma. irresp. of their ability to inhibit COX-2. Despite the fact that abnormally elevated COX-2 is associated with resistance to cell death, induction of apoptosis by certain NSAIDs is accompanied by up-regulation of COX-2 expression. This commentary focuses on dual effects of the typical PPAR.gamma. agonist 15d-PGJ2 on cell proliferation and growth, and its possible involvement in the NSAID-induced COX-2 expression and apoptosis.

REFERENCE COUNT: 87 THERE ARE 87 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 16 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2003:571131 CAPLUS Full-text

DOCUMENT NUMBER: 139:130392

TITLE: Rev-Erbα-overexpressing preadipocytes and method for identifying modulators of adipocyte differentiation

INVENTOR(S): Staels, Bart

PATENT ASSIGNEE(S): Genfit, Fr.

SOURCE: PCT Int. Appl., 69 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: French

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003060106	A1	20030724	WO 2003-FR157	20030117
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
FR 2834996	A1	20030725	FR 2002-582	20020118

FR 2834996	B1	20041203			
CA 2472016	A1	20030724	CA 2003-2472016		20030117
AU 2003216739	A1	20030730	AU 2003-216739		20030117
EP 1468078	A1	20041020	EP 2003-712261		20030117
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK					
JP 2005525099	T	20050825	JP 2003-560193		20030117
US 2005032064	A1	20050210	US 2004-501525		20040716
PRIORITY APPLN. INFO.:			FR 2002-582	A	20020118
			WO 2003-FR157	W	20030117

AB The invention concerns a method for identifying compds. capable of modulating adipocyte differentiation, which consists in contacting the compound to be tested with genetically modified pre-adipocyte cells overexpressing the Rev-Erbα receptor and measuring the adipocyte differentiation of said genetically modified cells with the adipocyte differentiation of same said genetically modified pre-adipocyte cells in the absence of said compound to be tested. The invention also concerns genetically modified pre-adipocyte cells overexpressing the Rev-Erbα receptor. Modulators of adipocyte differentiation thus identified may be used in treatment of diabetes, obesity, etc. Thus, PPAR γ was shown to activate transcription of the Rev-Erbα gene by binding to the DR2 response element of the Rev-Erbα gene promoter and Rev-Erbα was shown to be a promoter of adipocyte differentiation. Overexpression of the Rev-Erbα gene in cell line 3T3-L1 enhanced differentiation of these pre-adipocyte cells.

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 17 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:	2002:297882 CAPLUS Full-text
DOCUMENT NUMBER:	137:288699
TITLE:	Peroxisome proliferator-activated receptor-gamma agonists inhibit experimental allergic encephalomyelitis by blocking IL-12 production, IL-12 signaling and Th1 differentiation
AUTHOR(S):	Natarajan, C.; Bright, J. J.
CORPORATE SOURCE:	Division of Neuroimmunology, Department of Neurology, Vanderbilt University School of Medicine, Nashville, TN, 37212, USA
SOURCE:	Genes and Immunity (2002), 3(2), 59-70 CODEN: GEIMA2; ISSN: 1466-4879
PUBLISHER:	Nature Publishing Group
DOCUMENT TYPE:	Journal
LANGUAGE:	English

AB Peroxisome proliferator-activated receptor-gamma (PPAR.gamma.) is a nuclear receptor transcription factor that regulates adipocyte differentiation and glucose homeostasis. PPAR.gamma. agonists are potent therapeutic agents for the treatment of type 2 diabetes and obesity. PPAR.gamma. agonists also prevent inflammation in animal models, suggesting their use for the treatment of human inflammatory diseases. Exptl. allergic encephalomyelitis (EAE) is a Th1 cell-mediated inflammatory demyelinating disease model of multiple sclerosis (MS) and IL-12 plays a crucial role in the pathogenesis of EAE and MS. In this study we have examined the effect of PPAR.gamma. agonists on the pathogenesis of EAE. In vivo treatment of SJL/J mice with PPAR.gamma. agonists, 15-deoxyΔ12,14 prostaglandin J2 or ciglitazone, decreased the duration and clin. severity of active immunization and adoptive transfer models of EAE. PPAR.gamma. agonists inhibited EAE in association with a decrease in IL-12 production and differentiation of neural antigen-specific Th1 cells. In vitro treatment of activated T cells with PPAR.gamma. agonists inhibited IL-12-induced activation of JAK-STAT signaling pathway and Th1

differentiation. These findings highlight the fact that PPAR γ agonists regulate central nervous system inflammation and demyelination by inhibiting IL-12 production, IL-12 signaling and Th1 differentiation in EAE.

REFERENCE COUNT: 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 18 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:283625 CAPLUS Full-text
DOCUMENT NUMBER: 137:76293
TITLE: 85-kDa cPLA2 plays a critical role in PPAR -mediated gene transcription in human hepatoma cells
AUTHOR(S): Han, Chang; Demetris, A. Jake; Michalopoulos, George; Shelhamer, James H.; Wu, Tong
CORPORATE SOURCE: Department of Pathology, University of Pittsburgh School of Medicine, Pittsburgh, PA, 15213, USA
SOURCE: American Journal of Physiology (2002), 282(4, Pt. 1), G586-G597
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In an effort to understand the role of key eicosanoid-forming enzymes in the activation of peroxisome proliferator-activated receptor (PPAR), this study was designed to evaluate the possible contributions of cytosolic phospholipase A2 (cPLA2) and group IIA secretory phospholipase A2 (sPLA2) in the regulation of PPAR-mediated gene transcription in a human hepatoma cell line (HepG2). The HepG2 cells express both PPAR-α and -γ but not PPAR-β. Overexpression of cPLA2, but not group IIA sPLA2 in the HepG2 cells, caused a significantly increased PPAR-α/γ-mediated reporter activity. Antisense inhibition of cPLA2 resulted in a significantly decreased PPAR-α/γ activity. The PPAR-α/γ-induced gene transcription in the HepG2 cells was inhibited by the cPLA2 inhibitors Me arachidonyl fluorophosphonate and arachidonyltrifluoromethyl ketone, but not by the sPLA2 inhibitor LY311727. The expression of PPAR-α-mediated endogenous gene apolipoprotein A-II was increased in cells with overexpression of cPLA2, decreased in cells with antisense inhibition of cPLA2, but unaltered in cells with overexpression of group IIA sPLA2. The above results demonstrated an important role of cPLA2, but not group IIA sPLA2 in the control of PPAR activation. The cPLA2-mediated PPAR activation was likely mediated by arachidonic acid and prostaglandin E2. This study reveals a novel intracellular function of cPLA2 in PPAR activation in HepG2 cells. The cPLA2 thus may represent a potential therapeutic target for the control of PPAR-related liver and metabolic disorders such as obesity , lipid metabolic disorders, diabetes mellitus, and atherosclerosis.

REFERENCE COUNT: 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 19 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:202077 CAPLUS Full-text
TITLE: Nuclear receptors in obesity, diabetes and cardiovascular disease
AUTHOR(S): Evans, Ronald M.
CORPORATE SOURCE: Howard Hughes Medical Institute, The Salk Institute, La Jolla, CA, 92037, USA
SOURCE: Abstracts of Papers, 221st ACS National Meeting, San Diego, CA, United States, April 1-5, 2001 (2001) MEDI-176
CODEN: 69FZD4
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal; Meeting Abstract

LANGUAGE: English

AB Of the three known **PPAR** genes, the gamma isoform functions as an adipocyte differentiation factor and is the primary target of antidiabetes drugs such as Rezulin and Avandia, as well as the novel endogenous lipid **prostaglandin** J2. Our previous work suggests that **PPAR** gamma represents a common mol. link between **obesity**, diabetes and cardiovascular disease. In further exploring **PPAR** gamma function, we have recently identified two key target genes that influence lipid loading. The ABC A1 protein has recently been shown to be a mediator of cellular cholesterol and phospholipid efflux. We now show that **PPAR** gamma induces ABC A1 expression and cholesterol removal from macrophages. Ligand activation of **PPAR** gamma leads to primary induction of LXRa, which in turn, stimulates induction of ABC A1. To explore the genetic basis of PPARg action we have employed homologous recombination to disrupt the endogenous allele. **PPAR** gamma null mice display a surprisingly broad array of defects that include complete lipodystrophy. Thus, in addition to being a major pharmaceutical target, **PPAR** gamma appears to participate in a surprisingly broad array of developmental and physiol. programs.

L17 ANSWER 20 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2001:131609 CAPLUS Full-text

DOCUMENT NUMBER: 134:191011

TITLE: Peroxisome proliferator-activated receptor γ, the ultimate liaison between fat and transcription

AUTHOR(S): Rocchi, Stephane; Auwerx, Johan

CORPORATE SOURCE: Institut de Genetique et de Biologie Moleculaire et Cellulaire CNRS/INSERM/ULP, C.U. de Strasbourg, Illkirch, F-67404, Fr.

SOURCE: British Journal of Nutrition (2000), 84(Suppl. 2), S223-S227
CODEN: BJNUAV; ISSN: 0007-1145

PUBLISHER: CABI Publishing

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review with 51 refs. The peroxisome proliferator-activated receptor gamma (PPAR.gamma.) is nuclear receptor that controls the expression of a large number of genes involved in adipocyte differentiation, lipid storage and insulin sensitization. PPAR.gamma. is bound and activated by fatty acid derivs. and **prostaglandin** J2. In addition, thiazolidinediones, non-steroidal anti-inflammatory drugs are synthetic ligands and agonists of this receptor. This review addresses the role of PPAR.gamma. in **obesity** and diabetes.

REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 21 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2000:777808 CAPLUS Full-text

DOCUMENT NUMBER: 133:320256

TITLE: TNFα

AUTHOR(S): Miki, Hiroshi; Kadowaki, Takashi

CORPORATE SOURCE: Sch. Med., The Univ. Tokyo, Japan

SOURCE: Ensho to Men'eki (2000), 8(6), 638-645
CODEN: ENMEFA; ISSN: 0918-8371

PUBLISHER: Sentan Igakusha

DOCUMENT TYPE: Journal; General Review

LANGUAGE: Japanese

AB A review with 37 refs., on the pathophysiol. functions and transcriptional regulation of TNFα, functions of TNFα-converting enzyme, involvement of TNFα and its receptors in insulin resistance in **obesity**, inhibition of insulin signaling by TNFα, mechanisms of inhibition of NF-κB activation by 15-deoxy-

Δ12,14-PGJ2 (PPAR.gamma. ligand) and thiazolidinediones, decrease in PPAR.gamma. expression in inflammatory bowel diseases (ulcerative colitis, Crohn's disease, etc.), and inhibition of inflammatory cytokine expression by thiazolidinediones in the treatment of colitis.

L17 ANSWER 22 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:101180 CAPLUS Full-text
DOCUMENT NUMBER: 132:260733
TITLE: Peroxisome proliferator-activated receptor γ, the ultimate liaison between fat and transcription
AUTHOR(S): Rocchi, Stephane; Auwerx, Johan
CORPORATE SOURCE: Institut de Genetique et Biologie Moleculaire et Cellulaire, Illkirch, 67404, Fr.
SOURCE: International Congress Series (1999), 1181(Common Disease: Genetic and Pathogenetic Aspects of Multifactorial Diseases), 169-179
CODEN: EXMDA4; ISSN: 0531-5131
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 88 refs. The peroxisome proliferator-activated receptor γ (PPAR.gamma.) is nuclear receptor that controls the expression of a large number of genes involved in adipocyte differentiation, lipid storage and insulin sensitization. PPAR.gamma. is bound and activated by fatty acid derivs. and prostaglandin J2. In addition, thiazolidinediones, nonsteroidal anti-inflammatory drugs are synthetic ligands and agonists of this receptor. Recently several studies have shown that this nuclear receptor has a role expanding beyond metabolism (diabetes and obesity) with functions in cell cycle control, carcinogenesis, inflammation and atherosclerosis. This review addresses the role of PPAR.gamma. in these different processes.

REFERENCE COUNT: 88 THERE ARE 88 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 23 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:28213 CAPLUS Full-text
DOCUMENT NUMBER: 132:192021
TITLE: Peroxisome proliferator-activated receptor-γ: A versatile metabolic regulator
AUTHOR(S): Rocchi, Stephane; Auwerx, Johan
CORPORATE SOURCE: Institute of Genetics and Molecular, Illkirch, F-67404, Fr.
SOURCE: Annals of Medicine (Helsinki) (1999), 31(5), 342-351
CODEN: ANMDEU; ISSN: 0785-3890
PUBLISHER: Royal Society of Medicine Press Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 107 refs. The peroxisome proliferator-activated receptor-γ (PPAR.gamma.) is a nuclear receptor that controls the expression of a large array of genes involved in adipocyte differentiation, lipid storage and insulin sensitization. PPAR γ is bound and activated by prostaglandin J2 and fatty acid derivs., which are its natural ligands. In addition, thiazolidinediones and nonsteroidal anti-inflammatory drugs are synthetic ligands and agonists of this receptor. Several studies have recently shown that this nuclear receptor has a role expanding beyond metabolism (diabetes and obesity) with functions in cell cycle control, carcinogenesis, inflammation and atherosclerosis. This review addresses the role of PPAR.gamma. in these processes.

REFERENCE COUNT: 107 THERE ARE 107 CITED REFERENCES AVAILABLE FOR

THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 24 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:215418 CAPLUS Full-text
DOCUMENT NUMBER: 131:42983
TITLE: PPAR.gamma. activation in human endothelial cells increases plasminogen activator inhibitor type-1 expression: PPAR.gamma. as a potential mediator in vascular disease
AUTHOR(S): Marx, Nikolaus; Bourcier, Todd; Sukhova, Galina K.; Libby, Peter; Plutzky, Jorge
CORPORATE SOURCE: Vascular Medicine and Atherosclerosis Unit, Cardiovascular Division, Harvard Medical School, Brigham and Women's Hospital, Boston, MA, 02115, USA
SOURCE: Arteriosclerosis, Thrombosis, and Vascular Biology (1999), 19(3), 546-551
CODEN: ATVBFA; ISSN: 1079-5642
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Plasminogen activator inhibitor type-1 (PAI-1) is a major physiol. inhibitor of fibrinolysis, with its plasma levels correlating with the risk for myocardial infarction and venous thrombosis. The regulation of PAI-1 transcription by endothelial cells (ECs), a major source of PAI-1, remains incompletely understood. Adipocytes also produce PAI-1, suggesting possible common regulatory pathways between adipocytes and ECs. Peroxisomal proliferator-activated receptor-γ (PPAR)γ is a ligand-activated transcription factor that regulates gene expression in response to various mediators such as 15-deoxy-Δ12,14- prostaglandin J2 (15d-PGJ2) and oxidized linoleic acid (9- and 13-HODE). The present study tested the hypotheses that human ECs express PPAR.gamma. and that this transcriptional activator regulates PAI-1 expression in this cell type. The authors found that human ECs contain both PPAR.gamma. mRNA and protein. Immunohistochem. of human carotid arteries also revealed the presence of PPAR.gamma. in ECs. Bovine ECs transfected with a PPAR response element (PPRE)-luciferase construct responded to stimulation by the PPAR γ agonist 15d-PGJ2 in a concentration-dependent manner, suggesting a functional PPAR.gamma. in ECs. Treatment of human ECs with 15d-PGJ2, 9(S)-HODE, or 13(S)-HODE augmented PAI-1 mRNA and protein expression, whereas multiple PPAR.alpha. activators did not change PAI-1 levels. Introduction of increasing amts. of a PPAR γ expression construct in human fibroblasts enhanced PAI-1 secretion from these cells in proportion to the amount of transfected DNA. Thus, ECs express functionally active PPAR.gamma. that regulates PAI-1 expression in ECs. The results establish a role for PPAR.gamma. in the regulation of EC gene expression, with important implications for the clin. links between obesity and atherosclerosis.
REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 25 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:728650 CAPLUS Full-text
DOCUMENT NUMBER: 130:3276
TITLE: Methods for identifying ligands for nuclear hormone receptors
INVENTOR(S): Evans, Ronald M.; Forman, Barry Marc
PATENT ASSIGNEE(S): The Salk Institute for Biological Studies, USA
SOURCE: PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9849555	A1	19981105	WO 1998-US6446	19980401
W: AU, CA, JP				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2288978	A1	19981105	CA 1998-2288978	19980401
AU 9869458	A	19981124	AU 1998-69458	19980401
EP 979407	A1	20000216	EP 1998-915218	19980401
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.: US 1997-846620 A 19970429
WO 1998-US6446 W 19980401

AB Fatty acids (FAs) and their derivs. are essential cellular metabolites whose concns. must be closely regulated. This implies that regulatory circuits exist which can sense changes in FA levels. Indeed, the peroxisome proliferator activated receptor α (PPAR.alpha.) regulates lipid homeostasis and is transcriptionally activated by a variety of lipid-like compds. It remains unclear as to how these structurally-diverse compds. can activate a single receptor. In accordance with the present invention, there are provided conformation-based assays which screen activators for their ability to bind to PPARs (i.e., PPAR.alpha., PPAR δ and PPAR.gamma.) and induce DNA binding. It is shown here that specific FAs, eicosanoids and lipomodulatory agents are ligands for PPAR.alpha., PPAR.delta. and/or PPAR γ. Since altered FA levels are associated with obesity, atherosclerosis, hypertension and diabetes, PPARs may serve as mol. sensors which are central to the development and treatment of these metabolic disorders.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 26 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:225433 CAPLUS Full-text
DOCUMENT NUMBER: 129:407
TITLE: BRL 49653 blocks the lipolytic actions of tumor necrosis factor-α: A potential new insulin-sensitizing mechanism for thiazolidinediones
AUTHOR(S): Souza, Sandra C.; Yamamoto, Mia T.; Franciosa, Mark D.; Lien, Ping; Greenberg, Andrew S.
CORPORATE SOURCE: Jean Mayer Human Nutrition Research Center on Aging, Tufts University, Boston, MA, 02111, USA
SOURCE: Diabetes (1998), 47(4), 691-695
CODEN: DIAEAZ; ISSN: 0012-1797
PUBLISHER: American Diabetes Association
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Thiazolidinediones (TZDs) such as BRL 49653 are a class of antidiabetic agents that are agonists for the peroxisome proliferator-activated nuclear receptor (PPAR-γ2). In vivo, TZDs reduce circulating levels of free fatty acids (FFAs) and ameliorate insulin resistance in individuals with obesity and NIDDM. Adipocyte production of TNF-α is proposed to play a role in the development of insulin resistance, and because BRL 49653 has been shown to antagonize some of the effects of TNF-α, we examined the effects of TNF-α and BRL 49653 on adipocyte lipolysis. After a 24-h incubation of TNF-α (10 ng/mL) with 3T3-L1 adipocytes, glycerol release increased by .apprx.7-fold, and FFA release increased by .apprx.44-fold. BRL 49653 (10 μmol/l) reduced TNF-α-induced

glycerol release by .apprx.50% (P < 0.001) and FFA release by .apprx.90% (P < 0.001). BRL 49653 also reduced glycerol release by .apprx.50% in adipocytes pretreated for 24 h with TNF-α. Prolonged treatment (5 days) with either BRL 49653 or another PPAR -γ2 agonist, 15-d-Δ-12,14-prostaglandin J2 (15-dΔPGJ2), blocked TNF-α-induced glycerol release by .apprx.100%. Catecholamine (isoproterenol)-stimulated lipolysis was unaffected by BRL 49653 and 15-dΔPGJ2. BRL 49653 partially blocked the TNF-α-mediated reduction in protein levels of hormone-sensitive lipase and perilipin A, two proteins involved in adipocyte lipolysis. These data suggest a novel pathway that may contribute to the ability of the TZDs to reduce serum FFA and increase insulin sensitivity.

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 27 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:74260 CAPLUS Full-text
DOCUMENT NUMBER: 128:176398
TITLE: Prostaglandins promote and block adipogenesis through opposing effects on peroxisome proliferator-activated receptor γ
AUTHOR(S): Reginato, Mauricio J.; Krakow, Samuel L.; Bailey, Shannon T.; Lazar, Mitchell A.
CORPORATE SOURCE: Division of Endocrinology, University of Pennsylvania Medical Center, Philadelphia, PA, 19104, USA
SOURCE: Journal of Biological Chemistry (1998), 273(4), 1855-1858
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Fat cell differentiation is a crit. aspect of obesity and diabetes. Dietary fatty acids are converted to arachidonic acid, which serves as precursor of prostaglandins (PGs). PGJ2 derivs. function as activating ligands for peroxisome proliferator-activated receptor γ (PPAR.gamma.), a nuclear hormone receptor that is central to adipogenic determination The authors report that PGF2α blocks adipogenesis through activation of mitogen-activated protein kinase, resulting in inhibitory phosphorylation of PPAR.gamma.. Both mitogen-activated protein kinase activation and PPAR.gamma. phosphorylation are required for the anti-adipogenic effects of PGF2α. Thus, PG signals generated at a cell surface receptor regulate the program of gene expression required for adipogenesis by modulating the activity of a nuclear hormone receptor that is directly activated by other PG signals. The balance between PGF2α and PGJ2 signaling may thus be central to the development of obesity and diabetes.

REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1997:808815 CAPLUS Full-text
DOCUMENT NUMBER: 128:136363
TITLE: Activators of peroxisome proliferator-activated receptor γ have depot-specific effects on human preadipocyte differentiation
AUTHOR(S): Adams, Maria; Montague, Carl T.; Prins, Johannes B.; Holder, Julie C.; Smith, Stephen A.; Sanders, Louise; Digby, Jan E.; Sewter, Ciaran P.; Lazar, Mitchell A.; Chatterjee, V. Krishna K.; O'rahilly, Stephen
CORPORATE SOURCE: Department of Medicine, Addenbrookes Hospital, University of Cambridge, Cambridge, CB2 2QQ, UK

SOURCE: Journal of Clinical Investigation (1997), 100(12), 3149-3153
CODEN: JCINAO; ISSN: 0021-9738
PUBLISHER: Rockefeller University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Activation of peroxisome proliferator-activated receptor (PPAR) γ, a nuclear receptor highly expressed in adipocytes, induces the differentiation of murine preadipocyte cell lines. Recently, thiazolidinediones (TZDs), a novel class of insulin-sensitizing compds. effective in the treatment of non-insulin-dependent diabetes mellitus (NIDDM) have been shown to bind to PPAR.gamma. with high affinity. We have examined the effects of these compds. on the differentiation of human preadipocytes derived from s.c. and omental (Om) fat. Assessed by lipid accumulation, glycerol 3-phosphate dehydrogenase activity, and mRNA levels, subcultured preadipocytes isolated from either s.c. or Om depots did not differentiate in defined serum-free medium. Addition of TZDs (BRL49653 or troglitazone) or 15-deoxy Δ12,14 prostaglandin J2 (a natural PPAR.gamma. ligand) enhanced markedly the differentiation of preadipocytes from s.c. sites, assessed by all three criteria. The rank order of potency of these agents in inducing differentiation matched their ability to activate transcription via human PPAR.gamma.. In contrast, preadipocytes from Om sites in the same individuals were refractory to TZDs, although PPAR.gamma. was expressed at similar levels in both depots. The mechanism of this depot-specific TZD response is unknown. However, given the association between Om adiposity and NIDDM, the site-specific responsiveness of human preadipocytes to TZDs may be involved in the beneficial effects of these compds. on in vivo insulin sensitivity.

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 29 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1997:308235 CAPLUS Full-text
DOCUMENT NUMBER: 127:31900
TITLE: Hypolipidemic drugs, polyunsaturated fatty acids, and eicosanoids are ligands for peroxisome proliferator-activated receptors α and δ
AUTHOR(S): Forman, Barry Marc; Chen, Jasmine; Evans, Ronald M.
CORPORATE SOURCE: The Salk Institute for Biological Studies and Howard Hughes Medical Institute, Gene Expression Laboratory, La Jolla, CA, 92037, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (1997), 94(9), 4312-4317
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Fatty acids (FAs) and their derivs. are essential cellular metabolites whose concns. must be closely regulated. This implies that regulatory circuits exist which can sense changes in FA levels. Indeed, the peroxisome proliferator-activated receptor α (PPAR.alpha.) regulates lipid homeostasis and is transcriptionally activated by a variety of lipid-like compds. It remains nuclear as to how these structurally diverse compds. can activate a single receptor. A novel conformation-based assay that screens activators for their ability to bind to PPAR.alpha./δ and induce DNA binding has been developed. It is shown here that specific FAs, eicosanoids, and hypolipidemic drugs are ligands for PPAR.alpha. or PPAR δ. Because altered FA levels are associated with obesity, atherosclerosis, hypertension, and diabetes, PPARs may serve as mol. sensors that are central to the development and treatment of these metabolic disorders.

REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 30 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1996:716837 CAPLUS Full-text
DOCUMENT NUMBER: 126:5387
TITLE: Activation of the nuclear receptor peroxisome proliferator-activated receptor γ promotes brown adipocyte differentiation
AUTHOR(S): Tai, Tzu-Ann C.; Jennermann, Caroline; Brown, Kathleen K.; Oliver, Beverly B.; MacGinnitie, Marissa A.; Wilkison, William O.; Brown, H. Roger; Lehmann, Jurgen M.; Kliewer, Steven A.; et al.
CORPORATE SOURCE: Dep. Medicine, Univ. Chicago, Chicago, IL, 60637, USA
SOURCE: Journal of Biological Chemistry (1996), 271(47), 29909-29914
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Brown adipose tissue (BAT) functions in non-shivering and diet-induced thermogenesis via its capacity for uncoupled mitochondrial respiration. BAT dysfunction in rodents is associated with severe defects in energy homeostasis, resulting in **obesity** and hyperglycemia. Here, we report that the nuclear receptor peroxisome proliferator-activated receptor γ (**PPAR**.gamma.), a **prostaglandin** -activated transcription factor recently implicated as a central regulator of white adipose tissue differentiation, also regulates brown adipocyte function. **PPAR**.gamma. is abundantly expressed in both embryonic and adult BAT. Treatment of CD-1 rats with the **PPAR** γ-selective ligand BRL49653, an anti-diabetic drug of the thiazolidinedione class, results in marked increases in the mass of interscapular BAT. In vitro, BRL49653 induces the terminal differentiation of the brown preadipocyte cell line HIB-1B as judged by both changes in cell morphol. and expression of uncoupling protein and other adipocyte-specific mRNAs. These data demonstrate that **PPAR** γ is a key regulatory factor in brown adipocytes and suggest that **PPAR**.gamma. functions not only in the storage of excess energy in white adipose tissue but also in its dissipation in BAT.
REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 31 OF 48 MEDLINE on STN
ACCESSION NUMBER: 2006736572 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 17174223
TITLE: Lipoprotein-associated phospholipase A2 A379V variant is associated with body composition changes in response to exercise training.
AUTHOR: Wootton Peter T E; Flavell David M; Montgomery Hugh E; World Mike; Humphries Steve E; Talmud Philippa J
CORPORATE SOURCE: Centre for Cardiovascular Genetics, Department of Medicine, British Heart Foundation Laboratories, Rayne Building, Royal Free and University College London Medical School, 5 University Street, London WC1E 6JF, UK.. rmhapwo@ucl.ac.uk
SOURCE: Nutrition, metabolism, and cardiovascular diseases : NMCD, (2007 Jan) Vol. 17, No. 1, pp. 24-31. Electronic Publication: 2006-03-20.
Journal code: 9111474. E-ISSN: 1590-3729.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

(RANDOMIZED CONTROLLED TRIAL)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(CLINICAL TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200701
ENTRY DATE: Entered STN: 19 Dec 2006
Last Updated on STN: 5 Jan 2007
Entered Medline: 4 Jan 2007

AB Lipoprotein-associated PLA2 (Lp-PLA2) hydrolyses the sn-2 position of glycerophospholipids, in particular platelet activating factor (PAF), generating significant amounts of Lyso-PAF which in turn, via a remodelling pathway, can generate arachidonic acid (AA) from alkyl-acyl-glycerophosphorylcholine. AA is a precursor for prostaglandin synthesis, which regulates adipogenesis through the peroxisome proliferator-activated receptor subfamily. AA may also modulate skeletal muscle growth. We investigated the association of the PLA2G7 A379V variant with changes in body composition in a longitudinal study of 123 male Caucasian army recruits over 10 weeks of intensive physical training. There was no effect of genotype on baseline measures. However, after exercise training, homozygosity for the 379V allele was associated with a decrease in percentage adipose tissue mass (-3.61+/-1.14%), compared to AV (-1.67+/-0.38%) and AA (-1.09+/-0.24%) genotypes (p=0.01), and a significant mean increase (3.51+/-1.17%) in percentage lean mass, compared to AV (1.64+/-0.38%) and AA (1.10+/-0.24%) recruits (p=0.02). The association of this genotype with changes in body composition after training suggests a novel role for Lp-PLA2.

L17 ANSWER 32 OF 48 MEDLINE on STN
ACCESSION NUMBER: 2006731443 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 17168664
TITLE: Essential Fatty acids - a review.
AUTHOR: Das Undurti N
CORPORATE SOURCE: UND Life Sciences, 13800 Fairhill Road, Shaker Heights, OH 44120, USA.. undurti@hotmail.com
SOURCE: Current pharmaceutical biotechnology, (2006 Dec) Vol. 7, No. 6, pp. 467-82. Ref: 180
Journal code: 100960530. E-ISSN: 1873-4316.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200701
ENTRY DATE: Entered STN: 19 Dec 2006
Last Updated on STN: 10 Jan 2007
Entered Medline: 9 Jan 2007

AB Essential fatty acids (EFAs): cis-linoleic acid (LA) and alpha-linolenic acid (ALA) are essential for humans and their deficiency is rare in humans due to their easy availability in diet. EFAs are metabolized to their respective long-chain metabolites: dihomo-gamma-linolenic acid (DGLA), and arachidonic acid (AA) from LA; and eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) from ALA. Some of these long-chain metabolites form precursors to respective prostaglandins (PGs), thromboxanes (TXs), and leukotrienes (LTs), lipoxins (LXs) and resolvins. EFAs and their metabolites may function as endogenous angiotensin converting enzyme and HMG-CoA reductase inhibitors, nitric oxide enhancers, anti-hypertensives, and anti-atherosclerotic molecules. EFAs react with nitric oxide (NO) to yield respective nitroalkene derivatives that have cell-signaling actions via ligation and activation of peroxisome proliferator-activated receptors (PPARs). In several diseases such

as obesity, hypertension, diabetes mellitus, coronary heart disease, alcoholism, schizophrenia, Alzheimer's disease, atherosclerosis, and cancer the metabolism of EFAs is altered. Thus, EFAs and their derivatives have significant clinical implications.

L17 ANSWER 33 OF 48 MEDLINE on STN
ACCESSION NUMBER: 2006651128 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 16966336
TITLE: A novel positive feedback loop between peroxisome proliferator-activated receptor-delta and prostaglandin E2 signaling pathways for human cholangiocarcinoma cell growth.
AUTHOR: Xu Lihong; Han Chang; Wu Tong
CORPORATE SOURCE: Department of Pathology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania 15213, USA.
CONTRACT NUMBER: R01 CA102325 (NCI)
R01 CA106280 (NCI)
SOURCE: The Journal of biological chemistry, (2006 Nov 10) Vol. 281, No. 45, pp. 33982-96. Electronic Publication: 2006-09-11.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, N.I.H., EXTRAMURAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200612
ENTRY DATE: Entered STN: 7 Nov 2006
Last Updated on STN: 22 Dec 2006
Entered Medline: 21 Dec 2006

AB Peroxisome proliferator-activated receptor-delta (PPARdelta) is a nuclear receptor implicated in lipid oxidation and the pathogenesis of obesity and diabetes. This study was designed to examine the potential effect of PPARdelta on human cholangiocarcinoma cell growth and its mechanism of actions. Overexpression of PPARdelta or activation of PPARdelta by its pharmacological ligand, GW501516, at low doses (0.5-50 nM) promoted the growth of three human cholangiocarcinoma cell lines (CCLP1, HuCCT1, and SG231). This effect was mediated by induction of cyclooxygenase-2 (COX-2) gene expression and production of prostaglandin E2 (PGE2) that in turn transactivated epidermal growth factor receptor (EGFR) and Akt. In support of this, inhibition of COX-2, EGFR, and Akt prevented the PPARdelta-induced cell growth. Furthermore, PPARdelta activation or PGE2 treatment induced the phosphorylation of cytosolic phospholipase A2alpha (cPLA2alpha), a key enzyme that releases arachidonic acid (AA) substrate for PG production via COX. Overexpression or activation of cPLA2alpha enhanced PPARdelta binding to PPARdelta response element (DRE) and increased PPARdelta reporter activity, indicating a novel role of cPLA2alpha for PPARdelta activation. Consistent with this, AA enhanced the binding of PPARdelta to DRE, in vitro, suggesting a direct role of AA for PPARdelta activation. In contrast, although PGE2 treatment increased the DRE reporter activity in intact cells, it failed to induce PPARdelta binding to DRE in cell-free system, suggesting that cPLA2alpha-mediated AA release is required for PGE2-induced PPARdelta activation. Taken together, these observations reveal that PPARdelta induces COX-2 expression in human cholangiocarcinoma cells and that the COX-2-derived PGE2 further activates PPARdelta through phosphorylation of cPLA2alpha. This positive feedback loop plays an important role for cholangiocarcinoma cell growth and may be targeted for chemoprevention and treatment.

L17 ANSWER 34 OF 48 MEDLINE on STN
ACCESSION NUMBER: 2006573257 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 17003477
TITLE: Activated human T lymphocytes express cyclooxygenase-2 and produce proadipogenic prostaglandins that drive human orbital fibroblast differentiation to adipocytes.
AUTHOR: Feldon Steven E; O'loughlin Charles W; Ray Denise M; Landskroner-Eiger Shira; Seweryniak Kathryn E; Phipps Richard P
CORPORATE SOURCE: Department of Ophthalmology, University of Rochester, Rochester, NY 14642, USA.
CONTRACT NUMBER: DE011390 (NIDCR)
ES01247 (NIEHS)
EY014564 (NEI)
EY017123 (NEI)
T32-DE07165 (NIDCR)
SOURCE: The American journal of pathology, (2006 Oct) Vol. 169, No. 4, pp. 1183-93.
Journal code: 0370502. ISSN: 0002-9440.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, N.I.H., EXTRAMURAL)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200611
ENTRY DATE: Entered STN: 28 Sep 2006
Last Updated on STN: 19 Dec 2006
Entered Medline: 24 Nov 2006

AB The differentiation of preadipocyte fibroblasts to adipocytes is a crucial process to many disease states including obesity, cardiovascular, and autoimmune diseases. In Graves' disease, the orbit of the eye can become severely inflamed and infiltrated with T lymphocytes as part of the autoimmune process. The orbital fibroblasts convert to fat-like cells causing the eye to protrude, which is disfiguring and can lead to blindness. Recently, the transcription factor peroxisome proliferator activated receptor (PPAR)-gamma and its natural (15d-PGJ2) and synthetic (thiazolidinedione-type) PPAR-gamma agonists have been shown to be crucial to the in vitro differentiation of preadipocyte fibroblasts to adipocytes. We show herein several novel findings. First, that activated T lymphocytes from Graves' patients drive the differentiation of PPAR-gamma-expressing orbital fibroblasts to adipocytes. Second, this adipogenic differentiation is blocked by nonselective small molecule cyclooxygenase (Cox)-1/Cox-2 inhibitors and by Cox-2 selective inhibitors. Third, activated, but not naive, human T cells highly express Cox-2 and synthesize prostaglandin D2 and related prostaglandins that are PPAR-gamma ligands. These provocative new findings provide evidence for how activated T lymphocytes, through production of PPAR-gamma ligands, profoundly influence human fibroblast differentiation to adipocytes. They also suggest the possibility that, in addition to the orbit, T lymphocytes influence the deposition of fat in other tissues.

L17 ANSWER 35 OF 48 MEDLINE on STN
ACCESSION NUMBER: 2006553952 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 16842938
TITLE: Depot-specific prostaglandin synthesis in human adipose tissue: a novel possible mechanism of adipogenesis.
AUTHOR: Quinkler Marcus; Bujalska Iwona J; Tomlinson Jeremy W; Smith Dave M; Stewart Paul M
CORPORATE SOURCE: Division of Medical Sciences, Institute of Biomedical

Research, University of Birmingham, Queen Elizabeth Hospital, Birmingham, B15 2TH, UK.

SOURCE: Gene, (2006 Oct 1) Vol. 380, No. 2, pp. 137-43. Electronic Publication: 2006-06-10.
Journal code: 7706761. ISSN: 0378-1119.

PUB. COUNTRY: Netherlands

DOCUMENT TYPE: (COMPARATIVE STUDY)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200611

ENTRY DATE: Entered STN: 19 Sep 2006
Last Updated on STN: 8 Nov 2006
Entered Medline: 7 Nov 2006

AB Despite the magnitude of the **obesity** epidemic, the mechanisms that contribute to increases in fat mass and to differences in fat depots are still poorly understood. Prostanoids have been proposed as potent adipogenic hormones, e.g. metabolites of **prostaglandin** J2 (PGJ2) bind and activate PPARgamma. We hypothesize that an altered expression of enzymes in PGJ2 synthesis may represent a novel pathogenic mechanism in human **obesity**. We characterized adipose depot-specific expression of enzymes in PGJ2 synthesis, **prostaglandin** transporter and PPARgamma isoforms. Paired omental and subcutaneous adipose tissue samples were obtained from 26 women undergoing elective abdominal surgery and gene expression examined in whole tissue and cultured preadipocytes using an Affymetrix cDNA microarray technique and validated with quantitative real-time PCR. All enzymes involved in **prostaglandin** synthesis were expressed in both adipose tissues. Expression of **prostaglandin** synthase-1 (PGHS1), **prostaglandin** D synthase (PTGDS), human **prostaglandin** transporter (hPGT) and PPARgamma2 was higher in OM adipose tissue compared to SC, whereas 17beta-hydroxysteroid dehydrogenase 5 (AKR1C3) showed predominance in SC adipose tissue. In SC adipose tissue, PGHS1 mRNA expression increased with BMI. The differential, depot-specific expression of key enzymes involved in transport, synthesis and metabolism of **prostaglandins** may have an important impact upon fat cell biology and may help to explain some of the observed depot-specific differences. In addition, the positive correlation between PGHS1 and BMI offers the novel hypothesis that the regulation of PG synthesis may have a role in determining fat distribution in human **obesity**.

L17 ANSWER 36 OF 48 MEDLINE on STN

ACCESSION NUMBER: 2006528554 MEDLINE Full-text

DOCUMENT NUMBER: PubMed ID: 16844232

TITLE: PPARgamma antagonists reverse the inhibition of neural antigen-specific Th1 response and experimental allergic encephalomyelitis by Ciglitazone and 15-deoxy-Delta12,14-**prostaglandin** J2.

AUTHOR: Raikwar Himanshu P; Muthian Gladson; Rajasingh Johnson; Johnson Caroline N; Bright John J

CORPORATE SOURCE: Department of Neurology, Vanderbilt University Medical Center, Nashville, TN 37212, USA.

CONTRACT NUMBER: R01 NS42257-01A1 (NINDS)
R21 CA106207-01 (NCI)

SOURCE: Journal of neuroimmunology, (2006 Sep) Vol. 178, No. 1-2, pp. 76-86. Electronic Publication: 2006-07-17.
Journal code: 8109498. ISSN: 0165-5728.

PUB. COUNTRY: Netherlands

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, N.I.H., EXTRAMURAL)

LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 200611
ENTRY DATE: Entered STN: 6 Sep 2006
Last Updated on STN: 15 Nov 2006
Entered Medline: 14 Nov 2006

AB Peroxisome proliferator-activated receptor-gamma is a nuclear receptor transcription factor that regulates cell growth, differentiation and homeostasis. PPARgamma agonists have been used to treat obesity , diabetes, cancer and inflammation and recent studies have shown the protective effects of PPARgamma agonists on experimental allergic encephalomyelitis (EAE), a Th1 cell-mediated autoimmune disease model of multiple sclerosis (MS). Our studies have further demonstrated that the PPARgamma agonists, 15d-PGJ2 and Ciglitazone, inhibit EAE through blocking IL-12 signaling leading to Th1 differentiation and the PPARgamma deficient heterozygous mice (PPARgamma+/-) or those treated with PPARgamma antagonists develop an exacerbated EAE in association with an augmented Th1 response. In this study, we show that the PPARgamma antagonists, Bisphenol A diglycidyl ether (BADGE) and 2-chloro-5-nitro-N-(4- pyridyl)benzamide (T0070907), reverse the inhibition of EAE by the PPARgamma agonists, Ciglitazone and 15-Deoxy-Delta(12,14)- Prostaglandin J2, in C57BL/6 wild-type and PPARgamma+/- mice. The reversal of EAE by BADGE and T0070907 was associated with restoration of neural antigen-induced T cell proliferation, IFNgamma production and Th1 differentiation inhibited by Ciglitazone and 15d-PGJ2. These results suggest that Ciglitazone and 15d-PGJ2 ameliorate EAE through PPARgamma-dependent mechanisms and further confirm a physiological role for PPARgamma in the regulation of CNS inflammation and demyelination in EAE.

L17 ANSWER 37 OF 48 MEDLINE on STN
ACCESSION NUMBER: 2005679744 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 16367886
TITLE: Differentiation-dependent regulation of the cyclooxygenase cascade during adipogenesis suggests a complex role for prostaglandins.
AUTHOR: Xie Y; Kang X; Ackerman W E 4th; Belury M A; Koster C; Rovin B H; Landon M B; Kniss D A
CORPORATE SOURCE: Department of Obstetrics and Gynecology, Laboratory of Perinatal Research, The Ohio State University, College of Medicine and Public Health, Columbus, OH 43210, USA.
CONTRACT NUMBER: HD35581 (NICHD)
SOURCE: Diabetes, obesity & metabolism, (2006 Jan) Vol. 8, No. 1, pp. 83-93.
Journal code: 100883645. ISSN: 1462-8902.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, N.I.H., EXTRAMURAL)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200605
ENTRY DATE: Entered STN: 22 Dec 2005
Last Updated on STN: 4 May 2006
Entered Medline: 3 May 2006

AB AIM: A thorough understanding of the mechanisms of adipocyte differentiation and metabolism is important for the prevention and/or treatment of obesity and its complications, including type 2 diabetes mellitus. A complex role for prostaglandins (PGs) in adipogenesis is suggested. We examined the expression and cellular localization of enzymes in the cyclooxygenase (COX) cascade that synthesize PGs as well as the PG profile as a function of differentiation status in 3T3-L1 cells. METHODS: Murine 3T3-L1 preadipocytes were used as a

model for studies of adipocyte differentiation induced by a hormone cocktail and compared with the parental fibroblastic line NIH 3T3. Both cell lines were incubated in maintenance medium or differentiation medium. Nine days after differentiation, the expression of enzymes in the COX cascade was evaluated by immunoblot analysis, reverse transcriptase- polymerase chain reaction (RT-PCR) and immunocytochemistry, and PG formation was examined using enzyme immunoassay. RESULTS: A differentiation-dependent diminution of COX-1 and COX-2 mRNA and cognate proteins in 3T3-L1 cells was observed. PG release, including PGE(2), 6-keto PGF(1alpha), PGD(2) and 15d-PGJ(2), significantly decreased following differentiation in 3T3-L1 cells (anova/Tukey, $p < 0.05$). However, microsomal PGE synthase (mPGES) and lipocalin-type PGD synthase (L-PGDS) were selectively upregulated. Immunocytochemistry revealed that COX-1 and COX-2 became intracellularly more diffuse upon differentiation, whereas mPGES was redistributed to the nuclear compartment. CONCLUSIONS: Regulation of PG formation and COX-2 expression in 3T3-L1 cells is differentiation-dependent and involves changes in the levels of gene expression of the individual isoforms as well as redistribution of the enzymes within cellular compartments.

L17 ANSWER 38 OF 48 MEDLINE on STN

ACCESSION NUMBER: 2005160703 MEDLINE Full-text

DOCUMENT NUMBER: PubMed ID: 15684432

TITLE: The fatty acid-binding protein, aP2, coordinates macrophage cholesterol trafficking and inflammatory activity. Macrophage expression of aP2 impacts peroxisome proliferator-activated receptor gamma and IkappaB kinase activities.

AUTHOR: Makowski Liza; Brittingham Katherine C; Reynolds Joseph M; Suttles Jill; Hotamisligil Gokhan S

CORPORATE SOURCE: Department of Genetics and Complex Diseases, Harvard School of Public Health, Boston, Massachusetts 02115, USA.

CONTRACT NUMBER: F32 HL075970-01 (NHLBI)
R01 AI48850 (NIAID)

SOURCE: The Journal of biological chemistry, (2005 Apr 1) Vol. 280, No. 13, pp. 12888-95. Electronic Publication: 2005-01-31. Journal code: 2985121R. ISSN: 0021-9258.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200505

ENTRY DATE: Entered STN: 29 Mar 2005
Last Updated on STN: 14 May 2005
Entered Medline: 13 May 2005

AB Fatty acid-binding proteins are cytosolic fatty acid chaperones, and the adipocyte isoform, aP2, plays an important role in obesity and glucose metabolism. Recently, this protein has been detected in macrophages where it strongly contributes to the development of atherosclerosis. Here, we investigated the role of aP2 in macrophage biology and the molecular mechanisms underlying its actions. We demonstrate that aP2-deficient macrophages display defects in cholesterol accumulation and alterations in pro-inflammatory responsiveness. Deficiency of aP2 alters the lipid composition in macrophages and enhances peroxisome proliferator-activated receptor gamma activity, leading to elevated CD36 expression and enhanced uptake of modified low density lipoprotein. The increased peroxisome proliferator-activated receptor gamma activity in aP2-deficient macrophages is also accompanied by a significant stimulation of the liver X receptor alpha-

ATP-binding cassette transporter A1-mediated cholesterol efflux pathway. In parallel, aP2-deficient macrophages display reduced IkappaB kinase and NF-kappaB activity, resulting in suppression of inflammatory function including reduced cyclooxygenase-2 and inducible nitric-oxide synthase expression and impaired production of inflammatory cytokines. Our results demonstrate that aP2 regulates two central molecular pathways to coordinate macrophage cholesterol trafficking and inflammatory activity.

L17 ANSWER 39 OF 48 MEDLINE on STN
ACCESSION NUMBER: 2005055607 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 15539957
TITLE: WNT and cyclooxygenase-2 cross-talk accelerates adenoma growth.
AUTHOR: Wang Dingzhi; Mann Jason R; DuBois Raymond N
CORPORATE SOURCE: Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, USA.
CONTRACT NUMBER: P0-CA77839 (NCI)
R0-DK-62112 (NIDDK)
R37-DK47297 (NIDDK)
SOURCE: Cell cycle (Georgetown, Tex.), (2004 Dec) Vol. 3, No. 12, pp. 1512-5. Electronic Publication: 2004-12-06. Ref: 44
Journal code: 101137841. E-ISSN: 1551-4005.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, N.I.H., EXTRAMURAL)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200604
ENTRY DATE: Entered STN: 2 Feb 2005
Last Updated on STN: 14 Dec 2005
Entered Medline: 28 Apr 2006

AB Both Wnt and cyclooxygenase (COX-2) pathways are activated in most sporadic and familial colorectal cancers, especially in those with chromosomal instability. We have recently shown that a common target of both signaling pathways, the peroxisome proliferator-activated receptor (PPAR)-delta, is involved in intestinal adenoma growth. Activation of this receptor by synthetic agonist (GW501516) or COX-2-derived prostaglandin E2 (PGE2) accelerates intestinal adenoma growth in Apc(Min) mice. Moreover, these effects are lost in Apc(Min) mice lacking PPARdelta. These findings implicate PPARdelta as a focal point of cross-talk between the Wnt and prostaglandin signaling pathways. Based on this work it looks as if PPARdelta agonists currently in development for treatment of dyslipidemias and obesity may increase the risk of tumor formation in humans. By contrast, antagonists of PPARdelta may provide a novel approach for prevention and treatment of colorectal cancer.

L17 ANSWER 40 OF 48 MEDLINE on STN
ACCESSION NUMBER: 2003323259 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 12852255
TITLE: Peroxisome proliferator-activated receptors and the cardiovascular system.
AUTHOR: Chen Yuqing E; Fu Mingui; Zhang Jifeng; Zhu Xiaojun; Lin Yiming; Akinbami Mukaila A; Song Qing
CORPORATE SOURCE: Cardiovascular Research Institute, Morehouse School of Medicine, Atlanta, Georgia 30310, USA.

CONTRACT NUMBER: HL03676-02 (NHLBI)
R01HL068878 (NHLBI)
S06GM08248 (NIGMS)
SOURCE: Vitamins and hormones, (2003) Vol. 66, pp. 157-88. Ref: 188
Journal code: 0413601. ISSN: 0083-6729.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200307
ENTRY DATE: Entered STN: 11 Jul 2003
Last Updated on STN: 1 Aug 2003
Entered Medline: 31 Jul 2003

AB Insulin resistance syndrome (also called syndrome X) includes **obesity**, diabetes, hypertension, and dyslipidemia and is a complex phenotype of metabolic abnormalities. The disorder poses a major public health problem by predisposing individuals to coronary heart disease and stroke, the leading causes of mortality in Western countries. Given that hypertension, diabetes, dyslipidemia, and **obesity** exhibit a substantial heritable component, it is postulated that certain genes may predispose some individuals to this cluster of cardiovascular risk factors. Emerging data suggest that peroxisome proliferator-activated receptors (**PPARs**), including alpha, gamma, and delta, are important determinants that may provide a functional link between **obesity**, hypertension, and diabetes. It has been well documented that hypolipidemic fibrates and antidiabetic thiazolidinediones are synthetic ligands for **PPAR** alpha and **PPAR** gamma, respectively. In addition, **PPAR** natural ligands, such as leukotriene B4 for **PPAR** alpha, 15-deoxy-delta 12,14- **prostaglandin** J2 for **PPAR** gamma, and prostacyclin for **PPAR** delta, are known to be eicosanoids and fatty acids. Studies have documented that **PPARs** are present in all critical vascular cells: endothelial cells, vascular smooth muscle cells, and monocyte-macrophages. These observations suggest that **PPARs** not only control lipid metabolism but also regulate vascular diseases such as atherosclerosis and hypertension. In this review, we present structure and tissue distribution of **PPAR** nuclear receptors, discuss the mechanisms of action and regulation, and summarize the rapid progress made in this area of study and its impact on the cardiovascular system.

L17 ANSWER 41 OF 48 MEDLINE on STN
ACCESSION NUMBER: 2002165200 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 11897617
TITLE: 85-kDa cPLA(2) plays a critical role in PPAR -mediated gene transcription in human hepatoma cells.
AUTHOR: Han Chang; Demetris A Jake; Michalopoulos George; Shelhamer James H; Wu Tong
CORPORATE SOURCE: Department of Pathology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania 15213, USA.
SOURCE: American journal of physiology. Gastrointestinal and liver physiology, (2002 Apr) Vol. 282, No. 4, pp. G586-97.
Journal code: 100901227. ISSN: 0193-1857.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200204

ENTRY DATE: Entered STN: 19 Mar 2002
Last Updated on STN: 6 Apr 2002
Entered Medline: 5 Apr 2002

AB In an effort to understand the role of key eicosanoid-forming enzymes in the activation of peroxisome proliferator-activated receptor (PPAR), this study was designed to evaluate the possible contributions of cytosolic phospholipase A(2) (cPLA(2)) and group IIA secretory phospholipase A(2) (sPLA(2)) in the regulation of PPAR-mediated gene transcription in a human hepatoma cell line (HepG2). The HepG2 cells express both PPAR-alpha and -gamma but not PPAR-beta. Overexpression of cPLA(2), but not group IIA sPLA(2) in the HepG2 cells, caused a significantly increased PPAR-alpha/gamma-mediated reporter activity. Antisense inhibition of cPLA(2) resulted in a significantly decreased PPAR-alpha/gamma activity. The PPAR-alpha/gamma-induced gene transcription in the HepG2 cells was inhibited by the cPLA(2) inhibitors methyl arachidonyl fluorophosphonate and arachidonyltrifluoromethyl ketone, but not by the sPLA(2) inhibitor LY311727. The expression of PPAR-alpha-mediated endogenous gene apolipoprotein A-II was increased in cells with overexpression of cPLA(2), decreased in cells with antisense inhibition of cPLA(2), but unaltered in cells with overexpression of group IIA sPLA(2). The above results demonstrated an important role of cPLA(2), but not group IIA sPLA(2) in the control of PPAR activation. The cPLA(2)-mediated PPAR activation was likely mediated by arachidonic acid and prostaglandin E(2). This study reveals a novel intracellular function of cPLA(2) in PPAR activation in HepG2 cells. The cPLA(2) thus may represent a potential therapeutic target for the control of PPAR-related liver and metabolic disorders such as obesity, lipid metabolic disorders, diabetes mellitus, and atherosclerosis.

L17 ANSWER 42 OF 48 MEDLINE on STN
ACCESSION NUMBER: 2000476335 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 11026084
TITLE: [Adipose tissue and obesity].
Fettgewebe und Fettsucht.
AUTHOR: Kather H
CORPORATE SOURCE: Klinisches Institut fur Herzinfarktforschung, Medizinischen Universitatsklinik, Heidelberg.
SOURCE: Therapeutische Umschau. Revue therapeutique, (2000 Aug) Vol. 57, No. 8, pp. 488-92. Ref: 15
Journal code: 0407224. ISSN: 0040-5930.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: (ENGLISH ABSTRACT)
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: German
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200011
ENTRY DATE: Entered STN: 22 Mar 2001
Last Updated on STN: 22 Mar 2001
Entered Medline: 13 Nov 2000

AB Adipose tissue is not simply a storage depot. Adipocytes secrete hormones, growth factors and cytokines, such as leptin and TNF-alpha, as well as proteins that are related to the immune system and vascular functions. Through this network of endocrine, paracrine, and autocrine signals fat cells participate in the regulation of energy homeostasis, host defense and reproduction, and may also contribute to the development of pathological states, such as insulin resistance. Adipose tissue is confined to distinct depots. In Cushing's disease or following treatment of AIDS, certain adipose depots enlarge whereas others shrink, suggesting the existence of site-specific differences in fat cell function. Increases in adipocyte number occur via replication of preadipocytes, a process that is not restricted to infancy

but occurs throughout life. In contrast to still widely-held beliefs, mature fat cells can be eliminated by dedifferentiation or apoptosis. PPAR-gamma, a transcription factor that is activated by fatty acids and prostaglandins, plays a central role in adipose conversion of preadipocytes and appears to participate in controlling the size of mature fat cells as well.

L17 ANSWER 43 OF 48 MEDLINE on STN
ACCESSION NUMBER: 1999174104 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 10073956
TITLE: PPARgamma activation in human endothelial cells increases plasminogen activator inhibitor type-1 expression: PPARgamma as a potential mediator in vascular disease.
AUTHOR: Marx N; Bourcier T; Sukhova G K; Libby P; Plutzky J
CORPORATE SOURCE: Vascular Medicine and Atherosclerosis Unit, Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA.
CONTRACT NUMBER: HL03107 (NHLBI)
HL48743 (NHLBI)
SOURCE: Arteriosclerosis, thrombosis, and vascular biology, (1999 Mar) Vol. 19, No. 3, pp. 546-51.
Journal code: 9505803. ISSN: 1079-5642.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 20 Apr 1999
Last Updated on STN: 20 Apr 1999
Entered Medline: 2 Apr 1999

AB Plasminogen activator inhibitor type-1 (PAI-1) is a major physiological inhibitor of fibrinolysis, with its plasma levels correlating with the risk for myocardial infarction and venous thrombosis. The regulation of PAI-1 transcription by endothelial cells (ECs), a major source of PAI-1, remains incompletely understood. Adipocytes also produce PAI-1, suggesting possible common regulatory pathways between adipocytes and ECs. Peroxisomal proliferator-activated receptor-gamma (PPAR)gamma is a ligand-activated transcription factor that regulates gene expression in response to various mediators such as 15-deoxy-Delta12, 14- prostaglandin J2 (15d-PGJ2) and oxidized linoleic acid (9- and 13-HODE). The present study tested the hypotheses that human ECs express PPARgamma and that this transcriptional activator regulates PAI-1 expression in this cell type. We found that human ECs contain both PPARgamma mRNA and protein. Immunohistochemistry of human carotid arteries also revealed the presence of PPARgamma in ECs. Bovine ECs transfected with a PPAR response element (PPRE)-luciferase construct responded to stimulation by the PPARgamma agonist 15d-PGJ2 in a concentration-dependent manner, suggesting a functional PPARgamma in ECs. Treatment of human ECs with 15d-PGJ2, 9(S)-HODE, or 13(S)-HODE augmented PAI-1 mRNA and protein expression, whereas multiple PPARalpha activators did not change PAI-1 levels. Introduction of increasing amounts of a PPARgamma expression construct in human fibroblasts enhanced PAI-1 secretion from these cells in proportion to the amount of transfected DNA. Thus, ECs express functionally active PPARgamma that regulates PAI-1 expression in ECs. Our results establish a role for PPARgamma in the regulation of EC gene expression, with important implications for the clinical links between obesity and atherosclerosis.

L17 ANSWER 44 OF 48 MEDLINE on STN

ACCESSION NUMBER: 1998381941 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 9717841
TITLE: The short- and long-term effects of tumor necrosis factor-alpha and BRL 49653 on peroxisome proliferator-activated receptor (PPAR)gamma2 gene expression and other adipocyte genes.
AUTHOR: Rosenbaum S E; Greenberg A S
CORPORATE SOURCE: The USDA Human Nutrition Research Center on Aging at Tufts University, Tupper Medical Research Institute, New England Medical Center, Boston, Massachusetts 02111, USA.
CONTRACT NUMBER: P30 DK-40561 (NIDDK)
T32DK-07704 (NIDDK)
SOURCE: Molecular endocrinology (Baltimore, Md.), (1998 Aug) Vol. 12, No. 8, pp. 1150-60.
Journal code: 8801431. ISSN: 0888-8809.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199810
ENTRY DATE: Entered STN: 6 Jan 1999
Last Updated on STN: 18 Mar 2003
Entered Medline: 29 Oct 1998

AB Expression of tumor necrosis factor-alpha(TNFalpha) in adipocytes has been reported to correlate with insulin resistance associated with obesity. The thiazolidinediones such as BRL 49653 have been reported to improve insulin sensitivity in obese animals and humans. Although its exact mechanism of action is not known, BRL 49653 has been shown to antagonize some of the inhibitory actions of TNFalpha. BRL 49653 binds and activates the peroxisome proliferator-activated receptor (PPARgamma2), an important nuclear transcription factor in adipocyte differentiation; however, its regulation of PPARgamma2 in differentiated adipocytes is unknown. In this paper, we find that BRL 49653 blocked the ability of TNFalpha to down-regulate the expression and transcription of several adipocyte genes, but BRL 49653 did not prevent TNFalpha from down-regulating PPARgamma2. Moreover, BRL 49653 alone initially decreased the expression of PPARgamma2 mRNA and protein greatly. After 24 h of treatment in 3T3-L1 adipocytes, BRL 49653 down-regulated PPARgamma2 by greater than 90% and potentiated the decrease of PPARgamma2 mRNA by TNFalpha at this time. These unexpected results prompted us to repeat the experiments for a longer time to determine whether BRL 49653 would continue to down-regulate PPARgamma2. With prolonged BRL 49653 treatment, PPARgamma2 mRNA expression was not decreased as greatly, and the protein levels were decreased 20-30% below control at 72 h compared to 90% at 24 h. Although BRL 49653 continued to prevent the inhibitory effects of TNFgamma on perilipin and aP2 mRNA, by 72 h, BRL 49653 was not as potent an inhibitor of TNFalpha's down-regulation of perilipin protein. Since PPARgamma2 protein was more abundant at this time, these results suggest that the level of PPARgamma2 protein is not the sole factor that regulates the transcriptional control by BRL 49653.

L17 ANSWER 45 OF 48 MEDLINE on STN
ACCESSION NUMBER: 1998227657 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 9568706
TITLE: BRL 49653 blocks the lipolytic actions of tumor necrosis factor-alpha: a potential new insulin-sensitizing mechanism for thiazolidinediones.
AUTHOR: Souza S C; Yamamoto M T; Franciosa M D; Lien P; Greenberg A S
CORPORATE SOURCE: Jean Mayer Human Nutrition Research Center on Aging, Tufts

University, Boston, Massachusetts 02111, USA.
SOURCE: Diabetes, (1998 Apr) Vol. 47, No. 4, pp. 691-5.
Journal code: 0372763. ISSN: 0012-1797.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, U.S. GOV'T, NON-P.H.S.)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199805
ENTRY DATE: Entered STN: 14 May 1998
Last Updated on STN: 18 Mar 2003
Entered Medline: 7 May 1998

AB Thiazolidinediones (TZDs) such as BRL 49653 are a class of antidiabetic agents that are agonists for the peroxisome proliferator-activated nuclear receptor (PPAR-gamma2). In vivo, TZDs reduce circulating levels of free fatty acids (FFAs) and ameliorate insulin resistance in individuals with obesity and NIDDM. Adipocyte production of TNF-alpha is proposed to play a role in the development of insulin resistance, and because BRL 49653 has been shown to antagonize some of the effects of TNF-alpha, we examined the effects of TNF-alpha and BRL 49653 on adipocyte lipolysis. After a 24-h incubation of TNF-alpha (10 ng/ml) with 3T3-L1 adipocytes, glycerol release increased by approximately 7-fold, and FFA release increased by approximately 44-fold. BRL 49653 (10 pmol/l) reduced TNF-alpha-induced glycerol release by approximately 50% ($P < 0.001$) and FFA release by approximately 90% ($P < 0.001$). BRL 49653 also reduced glycerol release by approximately 50% in adipocytes pretreated for 24 h with TNF-alpha. Prolonged treatment (5 days) with either BRL 49653 or another PPAR-gamma2 agonist, 15-d delta-12,14- prostaglandin J2 (15-d deltaPGJ2), blocked TNF-alpha-induced glycerol release by approximately 100%. Catecholamine (isoproterenol)-stimulated lipolysis was unaffected by BRL 49653 and 15-d deltaPGJ2. BRL 49653 partially blocked the TNF-alpha-mediated reduction in protein levels of hormone-sensitive lipase and perilipin A, two proteins involved in adipocyte lipolysis. These data suggest a novel pathway that may contribute to the ability of the TZDs to reduce serum FFA and increase insulin sensitivity.

L17 ANSWER 46 OF 48 MEDLINE on STN
ACCESSION NUMBER: 1998152339 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 9491639
TITLE: [Molecular endocrinology of hereditary obesity].
L'endocrinologie moleculaire des obesites hereditaires.
AUTHOR: Christophe J
CORPORATE SOURCE: Laboratoire de Biochimie generale et humaine, Institut de Pharmacie, Universite libre de Bruxelles.
SOURCE: Bulletin et memoires de l'Academie royale de medecine de Belgique, (1997) Vol. 152, No. 4, pp. 189-94.
Journal code: 7608462. ISSN: 0377-8231.
PUB. COUNTRY: Belgium
DOCUMENT TYPE: (ENGLISH ABSTRACT)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: French
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199805
ENTRY DATE: Entered STN: 29 May 1998
Last Updated on STN: 29 May 1998
Entered Medline: 15 May 1998

AB The hypothalamic disorders of obesity include hyperphagia, a low central orthosympathetic tone (with reduced thermogenesis), vagal hyperinsulinism, low serotonin efficacy, a hyperactive hypothalamo-hypophyseal-adrenal axis, a hypoactive GHRH-GH-IGF axis and hypogonadism of central origin.

Hyperlipogenesis, glucose intolerance and excessive gluconeogenesis are secondary features. Most frequently the hypothalamic ARC reacts poorly to the leptin hypersecreted by adipose tissue, so that the local synthesis of NPY is unchecked. Fortunately, two **prostaglandins** derived from dietary arachidonic acid bind fat cell **PPAR** gamma and hepatic **PPAR** alpha. Both nuclear proteins are phosphorylated through an insulin pathway, thereby inhibiting the expression of genes favoring **obesity** and stimulating that of genes accelerating fatty acid oxidation. The array of dietetic and pharmacologic tools considered today is analyzed.

L17 ANSWER 47 OF 48 MEDLINE on STN
ACCESSION NUMBER: 1998113138 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 9442016
TITLE: **Prostaglandins** promote and block adipogenesis through opposing effects on peroxisome proliferator-activated receptor gamma.
AUTHOR: Reginato M J; Krakow S L; Bailey S T; Lazar M A
CORPORATE SOURCE: Department of Medicine, University of Pennsylvania Medical Center, Philadelphia 19104, USA.
CONTRACT NUMBER: DK49780 (NIDDK)
SOURCE: The Journal of biological chemistry, (1998 Jan 23) Vol. 273, No. 4, pp. 1855-8.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199803
ENTRY DATE: Entered STN: 12 Mar 1998
Last Updated on STN: 12 Mar 1998
Entered Medline: 3 Mar 1998

AB Fat cell differentiation is a critical aspect of **obesity** and diabetes. Dietary fatty acids are converted to arachidonic acid, which serves as precursor of **prostaglandins** (PGs). PGJ2 derivatives function as activating ligands for peroxisome proliferator-activated receptor gamma (**PPAR** gamma), a nuclear hormone receptor that is central to adipogenic determination. We report here that PGF2 alpha blocks adipogenesis through activation of mitogen-activated protein kinase, resulting in inhibitory phosphorylation of **PPAR** gamma. Both mitogen-activated protein kinase activation and **PPAR** gamma phosphorylation are required for the anti-adipogenic effects of PGF2 alpha. Thus, PG signals generated at a cell surface receptor regulate the program of gene expression required for adipogenesis by modulating the activity of a nuclear hormone receptor that is directly activated by other PG signals. The balance between PGF2 alpha and PGJ2 signaling may thus be central to the development of **obesity** and diabetes.

L17 ANSWER 48 OF 48 MEDLINE on STN
ACCESSION NUMBER: 97146694 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 8993550
TITLE: Discovery of ligands for the nuclear peroxisome proliferator-activated receptors.
AUTHOR: Willson T M; Lehmann J M; Kliewer S A
CORPORATE SOURCE: Department of Medicinal Chemistry, Glaxo Research Institute, Research Triangle Park, North Carolina 27709, USA.
SOURCE: Annals of the New York Academy of Sciences, (1996 Dec 27) Vol. 804, pp. 276-83.

Journal code: 7506858. ISSN: 0077-8923.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199702
ENTRY DATE: Entered STN: 27 Feb 1997
Last Updated on STN: 18 Mar 2003
Entered Medline: 10 Feb 1997

AB The identification of high-affinity ligands for PPAR gamma has revealed the role of this receptor as the molecular target for the antidiabetic activity of the thiazolidinediones. The surprising observation that agonists of an adipogenic transcription factor reverse the obesity-associated disease of diabetes highlights the power of using potent and selective ligands to study receptor-mediated biology. Similarly, the observation that PGD2 and its cyclopentenone metabolites compounds are microM PPAR ligands suggests that these receptors may have a physiological role in mediating prostaglandin signaling in the spleen.